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Recent Progress towards Transition Metal-Catalyzed Synthesis of γ-Lactams

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The occurrence of the γ-lactam unit in the framework of various biologically active compounds has greatly contributed to the design and development of new synthetic transformations to access this important structural motif. Among the numerous methods developed so far, those based on transition metal catalysis are of high value as they generally allow an efficient and selective access to functionalized γ-lactams under rather mild reaction conditions. An overview of the recent advances in this field is presented herein. Metal-catalyzed processes are reviewed by highlighting their specificity and applicability, and mechanistic rationale are presented when possible.

1. Introduction

The γ-lactam moiety can probably be considered as one of the most important heterocyclic motifs used in chemistry. It is indeed found in a very large number of bioactive natural and non natural molecules (Figure 1) and has therefore been used as a privileged structural subunit for the design of several pharmaceutical agents. In addition, γ-lactams also served as valuable building blocks for the synthesis of complex molecules due to their latent reactivity and the large panel of highly selective transformations they can undergo. The development of methodologies allowing their synthesis is therefore of major importance and various synthetic approaches to γ-lactam compounds have been established over the years among which are the expansion of β-lactams, formal [3+2] annulations, or Lewis acid catalyzed tandem reactions.

The development of efficient transition metal-catalyzed C-C and C-heteroatom bond-forming reactions is a central subject in...
current organic synthesis. In line with the renewed interest for \( \gamma \)-lactams in organic and medicinal chemistry, substantial progress has been recently made in the development of practical and efficient metal-catalyzed protocols to access this heterocyclic motif.

As a very limited number of reviews have been published on this topic, the aim of this paper is to highlight the recent advances made during the last ten years in the field of transition metal-catalyzed synthesis of \( \gamma \)-lactams. It should be pointed that this review is strictly limited to the synthesis of this motif and that other 5-membered cyclic amides, such as oxindoles and pthalimidines, are not discussed herein.

2. Rhodium catalysis

2.1. Rh-catalyzed intramolecular carbenoid C-H insertion

Since Doyle's pioneering work in the late 1980s, the rhodium-catalyzed intramolecular C-H insertion reaction of \( \alpha \)-diazooamides has emerged as one of the most attractive methods for the synthesis of a variety of \( \gamma \)-lactams. While of general interest, this approach often suffers from competitive reactions which result in the formation of regioisomers, including \( \beta \)- and \( \gamma \)-lactams, and/or stereoisomers. The ratio of products mainly depends on the nature of the substrates employed and the nature of ligands present on the rhodium complex used as catalyst. In particular, it was found that the nature of the substituent at position \( \alpha \) to the carbene carbon could significantly affect the chemoselectivity and regioselectivity of the C-H insertion reaction, as originally reported by Wee and Padwa. In a series of elegant studies, Jung and co-workers recently demonstrated that the presence of a phenylsulfonyl moiety at the \( \alpha \) position of the carbene carbon could allow the regio- and the stereocontrol of the Rh-catalyzed formation of highly functionalized \( \gamma \)-lactams. In this case, the phenylsulfonyl group was proposed not only to alter the electron density at the carbene center but also to exert a steric effect during the C-H activation. In the presence of 1 mol% \( \text{Rh}(\text{OAc})_2 \), the reaction of \( \alpha \)-diazoo-\( \alpha \)-(diaryl)phosphoryl)acetamides afforded the corresponding \( \gamma \)-lactams in moderate to good yields with a good stereocontrol of the trans diastereoselectivity (Scheme 2). Importantly, the introduction of the bulky diarylketophosphoryl group significantly suppressed the formation of \( \beta \)-lactam.

Additional studies showed that such an intramolecular C-H insertion reaction could proceed well even in water. For example, \( \gamma \)-lactam could be readily obtained in water at 80 °C from \( \alpha \)-diazoo-\( \alpha \)-(diaryl)phosphoryl)acetamides, thus highlighting the practicability of this methodology (Scheme 3).
In 2005, Wee and co-workers reported a Rh-catalyzed cyclization reaction to prepare $N$-(bis(trimethylsilyl)methyl) ($N$-BTMSM) $\gamma$-lactams 10. It was found that upon treatment with a Rh(II) catalyst, diazoamides 9 could be converted into the corresponding $\gamma$-lactams 10 in moderate to good yields (Scheme 4). It is worth mentioning that the bulky $N$-BTMSM group plays an important role in this cyclization reaction since it helps in efficiently controlling the conformation of the tertiary diazoamide substrate.

![Scheme 4](image)

Scheme 4 Synthesis of $N$-BTMSM protected $\gamma$-lactams 10 via Rh(II)-catalyzed C-H insertion reaction.

In subsequent work by the same group, they successfully extended the scope of the reaction to the use of $N$-BTMSM diazoamide substrates of type 12. As described in Scheme 5, the Rh-catalyzed transformation furnished in this case highly functionalized trisubstituted $\gamma$-lactams 13 with good to excellent regio-, chemo-, and diastereoselectivities. In this case, the regioselectivity of the reaction could be explained not only by the presence of the BTMSM group but also by the electronic effect exerted by the OR group. It was also proposed that the choice of the rhodium catalyst was crucial to perform an effective control of the product distribution. The synthetic utility of this methodology was highlighted by the total synthesis of $\alpha$-allokainic acid 14.

![Scheme 5](image)

Scheme 5 Rh(II)-carbenoid-mediated synthesis of $\gamma$-lactams 13 from $N$-BTMSM diazoamides 12.

2.2. Rh-catalyzed multicomponent-coupling reaction

Rhodium-catalyzed multicomponent-coupling reactions have been employed as a mild and efficient way to generate new carbon-carbon bonds. Application of this strategy to the preparation of functionalized $\gamma$-lactams was investigated in 2006 by Shintani and Hayashi. It was found that the three-molecule four-component coupling reaction of 1,6-enyne 15, phenylzinc chloride, and iodomethane in the presence of a rhodium catalyst could lead to the formation of $\gamma$-lactams 16 in good yields (Scheme 6).

![Scheme 6](image)

Scheme 6 Synthesis of $\gamma$-lactams 16 via rhodium-catalyzed multicomponent-coupling reaction.

The reaction presumably proceeds following a two-step carborydation-alkylation-transmetalation sequence, as shown in Scheme 7.

![Scheme 7](image)

Scheme 7. Plausible catalytic cycle for the rhodium-catalyzed synthesis of $\gamma$-lactams 16.

2.3. Rh-catalyzed reductive cyclization of acetylenic aldehydes

Transition metal-catalyzed reductive coupling of alkynes with aldehydes has received considerable attention during the recent years, as it represents a powerful and efficient way to generate new C–C bonds. In 2006, Krische and co-workers reported that such a type of transformation could be used to produce $\gamma$-lactams in an enantioselective manner (Scheme 8). It was indeed found that the reductive cyclization of acetylenic aldehydes 17 into functionalized $\gamma$-lactams 18 could be efficiently performed in the presence of a rhodium catalyst under an atmosphere of hydrogen. Moderate to good yields and excellent enantioselectivities were obtained when ($R$)-Cl,MeO-BIPHEP was used as the ligand. Deuterium labelling studies revealed that the reaction might proceed via an oxidative coupling, followed by a hydrogenolytic cleavage of the resulting metallacycle involving a $\sigma$ bond metathesis.

![Scheme 8](image)

Scheme 8 Synthesis of chiral $\gamma$-lactams 18 via rhodium-catalyzed asymmetric hydrogenation.

2.4. Rh-catalyzed oxidative cyclization of dynes and enynes
Very recently, Tang and co-workers have shown that a Rh(I) catalyst could be used in combination with a pyridine oxide to transform N-tosylamide derivatives 19 into unsaturated or cyclopropane ring fused γ-lactams of types 20 and 21 (Scheme 9). This oxidative cyclization proved to be efficient (56-88%) and allows a rapid and practical access to a variety of functionalized γ-lactam derivatives under mild oxidative conditions. Structurally similar fused γ-lactams could also be obtained under oxidative conditions using a Pd catalyst (see Section 4.2).

The following mechanism has been proposed to explain the formation of compounds 20 and 21 (Scheme 10). An initial Rh-catalyzed nucleophilic addition of the pyridine oxide onto the alkyne moiety in 19, followed by extrusion of pyridine, generate the key rhodium carbenoid I. Interaction of this latter with the pendant alkyne or alkene chain generates the corresponding new rhodium carbenoid II which is then oxidized to produce 20, or the cyclopropyl derivative 21.

Another interesting procedure for the preparation of γ-lactams via ruthenium catalysis was described by Maas and co-workers in 2006. By using dinuclear ruthenium complexes of type [Ru2(CO)6(μ-L1)2L23] as the catalysts, they found that N,N-dialkyldiazoacetamides 25 could be converted into γ-lactams 26 in moderate to excellent yields (Scheme 12). While being generally selective, this C-H bond insertion reaction also furnished in some cases β-lactams 27 as minor products.

### 3. Ruthenium catalysis

#### 3.1. Ru-catalyzed intramolecular carbenoid C-H Insertion

Although extensive efforts have been directed towards the development of metal-catalyzed γ-lactams synthesis by intramolecular carbenoid C-H insertion reactions using α-diazoacarbonyl substrates, relatively little work has been carried out regarding the possibility to use other metal than rhodium in such transformations. In 2005, Yu and co-workers reported that α-diazoacetamides 22 could undergo smooth cyclization to give the corresponding γ-lactams 23 in serviceable yields albeit with minor cis-β-lactams 24 (Scheme 11). Notably, this Ru-catalyzed reaction, which corresponds to an intramolecular carbenoid insertion into aromatic C-H bond, did not require a slow addition of the diazo compound nor the use of an inert atmosphere.

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3.3. Ru-catalyzed asymmetric transfer hydrogenation of N-(tert-butyloxysulfinyl)iminoesters

Very recently, Gujjarro and co-workers reported a concise synthesis of chiral γ-lactam derivatives that involves a Ru-catalyzed asymmetric transfer hydrogenation reaction. Treatment of N-(tert-butyloxysulfinyl)iminoester 32 with a ruthenium catalyst in the presence of 2-amino-2-methylpropan-1-ol as a ligand and isopropanol alcohol as a hydrogen source produced the corresponding chiral γ-lactams 33 in excellent yields and enantioselectivities (Scheme 14).28

![Scheme 14 Synthesis of γ-lactams 33 by asymmetric transfer hydrogenation of N-(tert-butyloxysulfinyl)iminoesters 32.](image)

3.4. Ru-catalyzed asymmetric auto-tandem allylic amidation/ATRC reaction

Another interesting Ru-catalyzed asymmetric synthesis of γ-lactams was recently reported by Okamura and Onitsuka.29 It was found that the reaction of allylic chloride 34 with α-bromoamide 35 in the presence of planar-chiral Cp’Ru complex (S)-37 could furnish the chiral γ-lactams 36 in good to excellent yields and mostly excellent enantioselectivities. The authors extended the scope of the reaction to the use of α-dichloroamide 38 as the substrates. In this case, the reaction delivered the corresponding chiral γ-lactam derivatives 39 which possess three consecutive stereogenic centers in moderate yields (Scheme 15).

![Scheme 15 Synthesis of chiral γ-lactams 36 and 39 by asymmetric auto-tandem catalysis.](image)

The reaction presumably involves an asymmetric auto-tandem catalysis, consisting of an asymmetric allylic substitution (RuII/RuIV) and a diastereoselective atom-transfer radical cyclization (ATRC, RuIII/RuIV), as depicted in Scheme 16.

![Scheme 16 Proposed reaction mechanism of asymmetric auto-tandem catalysis.](image)

4. Palladium catalysis

4.1. Pd-catalyzed intramolecular allylation

In 2005, Craig and co-workers disclosed another elegant example of palladium-catalyzed synthesis of γ-lactams. It was found that the treatment of allylic carbonates 40 by a Pd(0) catalyst allowed the formation cis-4,5-disubstituted γ-lactams 41 in good yields (Scheme 17).30 This Pd-catalyzed intramolecular allylation provides a novel route to construct polysubstituted γ-lactams in a diastereoselective manner.

![Scheme 17 Pd-catalyzed intramolecular allylation for the construction of polysubstituted γ-lactams carbonates 41.](image)

4.2. Pd-catalyzed oxidation reaction of enyne

In 2007, an elegant method for the synthesis of γ-lactams from 1,6-enynes under Pd catalysis was reported by Sanford and co-workers. This oxidation reaction offers a concise and practical way for the stereospecific preparation of γ-lactams fused with a cyclopropane ring. As an example of this new protocol,
treatment of N-methyl-3-phenyl-N-vinylpropiolamide 42 with 5 mol% of Pd(OAc)$_2$, 6 mol% of bipy and 1.1 equiv of Phl(OAc)$_2$ in acetic acid led to the isolation of $\gamma$-lactam 43 in 47% yield (Scheme 18).$^{31}$

The authors rationalize this transformation by the mechanism depicted in Scheme 19. The alkenyl-Pd intermediate I is first formed by a trans acetoxypalladation of enyne 42. A subsequent intramolecular olefin insertion followed by an oxidation with Phl(OAc)$_2$ provides the key Pd(IV) intermediate III. $\gamma$-lactam 43 is finally produced following a reductive substitution type reaction after an attack of the vinyl acetate moiety on the carbon bonded to the Pd(IV) fragment.

The mechanism shown in Scheme 21 was proposed to explain the formation $\gamma$-lactam 45. An initial oxidative addition of the aryl iodide on Pd(0) generates the aryl palladium electrophilic species I, which then coordinates to the allene moiety of the substrate sodium salt 44. A subsequent carboxypalladation affords the $\pi$-allyl intermediate III, which is then trapped by the internal active methylene to afford the 5-exo cyclization $\gamma$-lactams 45.

4.3. Pd-catalyzed allene carboxypalladation/allylic alkylation reaction

In 2009, Prestat and Poli described a general route for the regio- and stereoselective synthesis of 4-(a-styryl) $\gamma$-lactams involving a phosphine-free Pd-catalyzed allene carboxypalladation/allylic alkylation domino sequence. As outlined in Scheme 20, the linear allenyl amide precursor 44 reacted with a variety of aryl iodides (electron-rich or electron-poor) to furnish the corresponding $\gamma$-lactams 45 in moderate to good yields (61-88%).$^{32}$ This methodology was readily used in the facile synthesis of $\gamma$-lactam 46, a racemic aza analogue of the naturally occurring lignan (+)-oxo-parabenzlactone 47.

4.4. Pd-catalyzed olefination of sp$^3$ C-H bonds

A palladium-catalyzed C-H olefination reaction has also been employed to construct $\gamma$-lactam derivatives (Scheme 22). In 2010, Yu and co-workers demonstrated that the reaction of CONHAr amides 48 with benzyl acrylate could afford the corresponding $\gamma$-lactams 50 in moderate to good yields.$^{33}$ The formation of 50 could be explained by an initial selective sp$^3$ C-H activation producing intermediate 49, which undergoes a subsequent intramolecular 1,4-conjugate addition.
moderate to good yields (Scheme 23). This procedure involves the use of NFSI and bathocuproine (7.5 mol%), 4-nitrophenol (20 mol%) and excess of PrOH in DMA to afford the fluorinated γ-lactams (Scheme 22). The mechanism proposed for this Pd-catalyzed tandem fluorination and cyclization of enynes involves the formation of a vinyl fluoro intermediate via the triple bond that generates a vinyl fluoro intermediate. This intermediate then undergoes an intramolecular alkene insertion to produce a new intermediate, which is then reduced to produce the fluorinated γ-lactam. It should be mentioned that the fluoropalladation step is cis-selective and that the subsequent cyclization step predominantly produces the E isomer of compound 52.

The mechanism proposed for this Pd-catalyzed tandem fluorination and cyclization of enyne is presented in Scheme 24. The reaction is initiated by a favorable cis-fluoropalladation of the triple bond that generates a vinyl fluoro intermediate. The latter undergoes an intramolecular alkene insertion to produce a new intermediate, which is then reduced in the presence of PrOH to finally deliver the fluorinated γ-lactam.

5. Gold catalysis

5.1. Au-catalyzed hydroamination of alkenes

In the last decade, homogeneous gold catalysis has proven to be a powerful tool in organic synthesis, leading to the formation of an incredible variety of different heterocyclic motifs. The application of gold catalysis to the construction of the versatile γ-lactam motif was recently investigated. In 2006, Che et al. described a new procedure for the synthesis of γ-lactam derivatives by an Au(I)-catalyzed intramolecular hydroamination of alkenes (Scheme 25). Treatment of benzamides 53 in the presence of 20 mol% Ph3PAuOTf in toluene produced the corresponding γ-lactams 54 in moderate yields. Notably, excellent yields could be achieved by employing a stoichiometric amount of Ph3PAuOTf.

5.2. Au-catalyzed intramolecular addition of β-ketoamide to unactivated alkenes

In 2007, Che et al. successfully used an analogous catalytic system to synthesize a variety of γ-lactams via an Au(I)-catalyzed intramolecular addition of a β-ketoamide to an unactivated alkene (Scheme 26). It was found that in the presence of 5 mol% of the Au[Pt(II)]Cl2(biiphenyl)]Cl/AgOTf catalytic system, β-ketoamides 55 could be cyclized into the highly substituted γ-lactams 56 in excellent yields.
the reaction can be performed in aqueous media and is amenable to the large-scale preparation of γ-lactams. This transformation was the first reported one to show the potential of gold to catalyze the intramolecular addition of 1,3-dicarbonyl moiety onto unactivated alkenes.

The formation of γ-lactams 58 was explained by the interception of a postulated gold carbenoid I by the pendent alkene chain (Scheme 29). Reactive intermediate I is supposed to be generated after a gold-catalyzed pyridine oxide addition on the alkyne in 57 followed by elimination of the pyridine moiety.

Very recently, Li and co-workers also demonstrated a similar oxidative cyclization of 1,5-enynes of type 59 to produce the cyclopropane fused γ-lactams 60 (Scheme 30). It should be mentioned that a range of functional groups including esters, aryl or acyl groups were tolerated under the acidic reaction conditions employed.

The proposed mechanism of the gold-catalyzed oxidative cyclization of 1,5-enynes is presented in scheme 31. Firstly, pyridine N-oxide attacks the gold-activated N-allylamides 59 to generate vinyl gold intermediate I. Subsequent intramolecular nucleophilic addition of an alkyn moiety and loss of pyridine allow the formation of intermediate II, which can be further transformed into the final product 60 and regenerate the gold catalyst.

5.3. Au-catalyzed oxidation-cyclopropanation sequence of enynes

In 2011, Zhang and Qian reported an interesting oxidative cyclization of 1,6-enynes of type 57 in the presence of a gold(I) catalyst and a pyridine oxide (Scheme 28). It is noteworthy that this transformation is efficient and leads to cyclopropane fused γ-lactams 58 which share noticeable structural similarities with those which can be obtained under Rh or Pd catalysis (see Section 2.4 and 4.2).

The mechanism of this interesting process is shown in Scheme 27. The cationic gold(I) complex first coordinates to substrate 55 to produce the alkene gold-(I) complex 56, which is proto-demetalated to finally afford γ-lactam 56 with regeneration of the gold catalyst.
5.5. Au-catalyzed tandem cycloisomerization/oxidation of homopropargyl amides

Recently, Ye and co-workers developed a new gold-catalyzed tandem cycloisomerization/oxidation reaction for the synthesis of γ-lactams under mild conditions (Scheme 32).\(^{40}\) Notably, this approach provides an expedient and general way for the preparation of a variety of optically active N-tosyl γ-lactams \(^{62}\) from readily available chiral homopropargyl amides \(^{61}\). The synthetic interest of this methodology was highlighted by the enantioselective total synthesis of natural product (-)-bguaine \(^{62}\).

The formation of γ-lactams \(^{62}\) could be explained by a gold-catalyzed oxycyclization producing vinyl gold intermediate, followed by an acid-accelerated oxidation (Scheme 33).

5.6. Au-catalyzed formal 1,6-acyloxy migration

Very recently, Hashimi and co-workers reported an unprecedented route based on a gold-catalyzed formal 1,6-acyloxy migration of propargylic esters for the synthesis of 3,4-disubstituted γ-lactams (Scheme 34).\(^{41}\) It was indeed found that in the presence 5 mol% of the [IPrAuCl]/AgSbF\(_6\) catalytic system, a large variety of propargylic esters \(^{64}\) could be transformed into 3,4-disubstituted pyrrolidin-2-ones \(^{65}\) in good to excellent yields (43-92%). On the basis of this work, the same group also reported the similar gold-catalyzed formal 1,6-phosphatyoxy migration and 1,6-carbonate migration.\(^{42}\)

6. Copper catalysis

6.1. Copper-catalyzed intramolecular vinylation of amides

In 2005, Li and co-workers disclosed a mild and efficient protocol for the CuI-catalyzed intramolecular coupling of amides, with iodoalkenes to produce N-alkenyl lactams in moderate to excellent yields. For example, treatment of 4-iodo-N-phenylpent-4-enamide \(^{66}\) with a catalytic amount of CuI (10 mol%) and \(N,N'-\)dimethylmethylenediamine (20 mol%) led to the formation of the N-vinyl γ-lactam \(^{67}\) which was isolated in 95% yield (Scheme 36).\(^{43}\) Six- and seven-membered lactams could also be produced using this protocol.
7. Cobalt catalysis.

7.1. Co-catalyzed reductive coupling of nitriles with acrylamides

During the last decade, a lot of attention has been brought to the development of metal-catalyzed regioselective reductive coupling (RRC). Indeed, this type of transformation allows the synthesis of highly functionalized products in a generally step- and atom- economical manner. In 2009, Cheng and co-workers disclosed a new type of Co-catalyzed reductive coupling for the preparation of γ-lactams. They discovered that the reaction of nitriles with a variety of acrylamides in the presence of 10 mol% of Co(dppe)I₂ and zinc could produce γ-lactams in moderate to excellent yields (Scheme 37). 

A proposed mechanism for the formation of lactams is depicted in Scheme 38. The Co(II) precatalyst is first reduced by zinc to furnish a catalytically active Co(I) species. Coordination of nitrile and acrylamide to Co(I), followed by a regioselective cyclometalation, produces the cobaltazacyclopentene intermediate I. A subsequent protonation of I furnishes the linear ketoamide II and a Co(III) species which can then be reduced by zinc to regenerate the active Co(I) species. A final cyclization of II delivers the γ-lactam derivatives 70.

8. Silver catalysis

8.1. Ag-catalyzed radical aminofluorination of unactivated alkenes

Very recently, Li and co-workers disclosed a rapid approach to γ-lactams based on an Ag(I)-catalyzed radical aminofluorination reaction. It was found that the fluoro γ-lactams could be synthesized under mild reaction conditions by an intramolecular cyclization of unactivated amidoalkenes involving the amidyl radical and in the transfer of the fluorine atom, was postulated to explain the formation of fluoro γ-lactams (Scheme 39).

The following reaction mechanism, in which silver is involved in the generation of the amidyl radical and in the transfer of the fluorine atom, was postulated to explain the formation of fluoro γ-lactams (Scheme 40).
9. Conclusions

During the last decade, transition metal catalysis has proven to be a particularly powerful and highly versatile synthetic tool for the construction of polyfunctionalized γ-lactams. The methodologies which have been recently developed to access this structural motif are varied. They involve catalytic systems based on the use of different transition metal, proceed generally under mild experimental conditions and are most of the time efficient and selective. Their synthetic interest has already been demonstrated, for some of them, through the total or formal synthesis of bioactive natural products. However, despite the numerous efforts recently made in this field, one has to admit that several aspects still need to be improved. This is more especially the case of the substrate scope and the functional group tolerance which should be extended, the nature of the catalytic systems which require more modularity and practicability, and the possibility to perform enantioselective transformations, which are still very limited. Given the increasing interest in the use of γ-lactams in chemistry and the fundamental synthetic potential of transition metal catalysis, one can imagine that even more new advances that will benefit both to academic and industrial chemists, will be made in the next decades.

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Notes and references

1 A simple SciFinder search concerning the use of γ-lactams in biological activity studies retrieved more than 310000 hits.


