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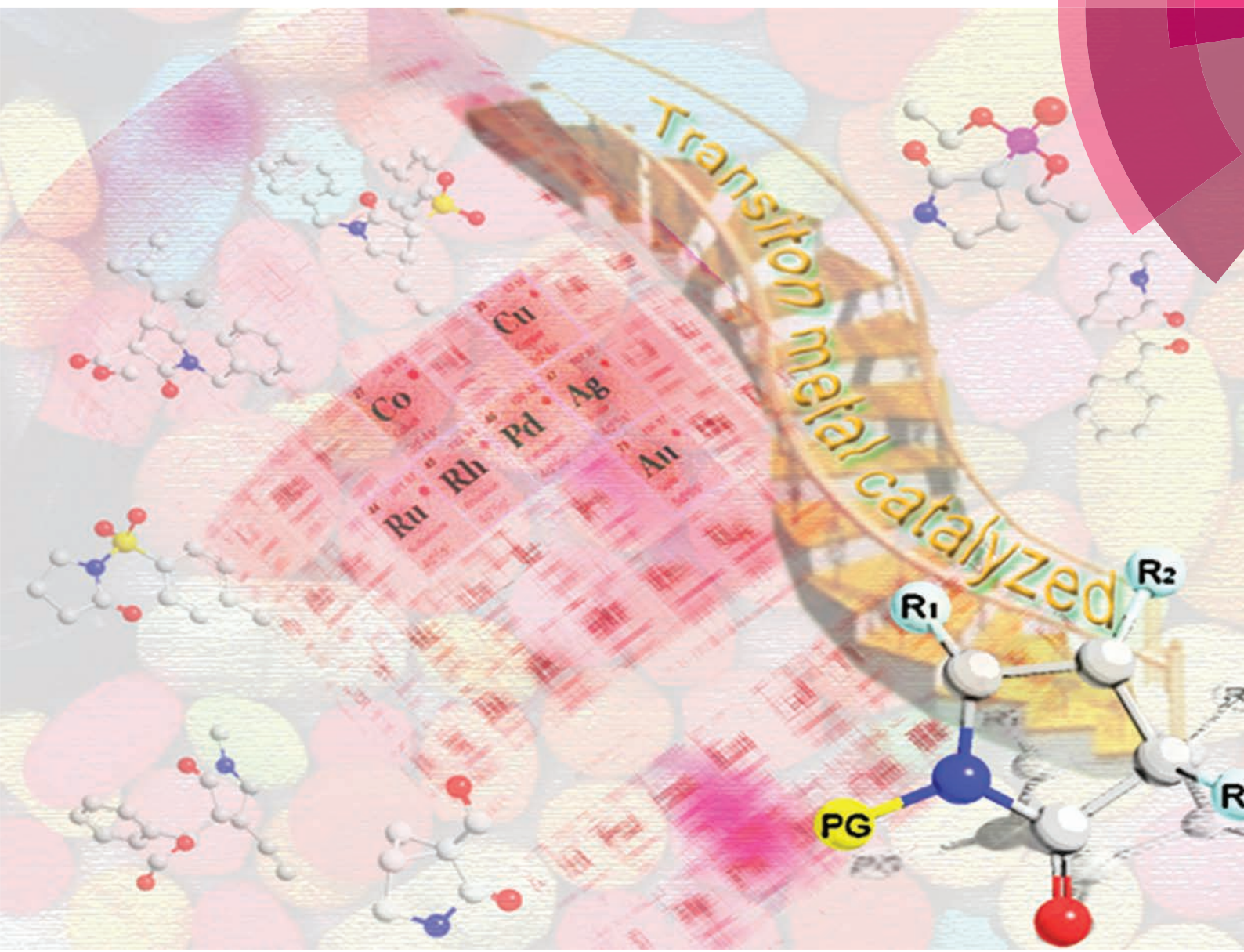

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Recent progress towards transition metal-catalyzed synthesis of γ-lactams

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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 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 the mechanistic rationale is presented where 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 (Fig. 1) and has therefore been used as a privileged structural subunit for the design of several pharmaceutical agents.[1,2] 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.[3] The development of methodologies allowing their synthesis is therefore of major importance and various synthetic approaches[4] to γ-lactam compounds have been established over the years, among which are the expansion of β-lactams,[5] formal [3 + 2] annulations,[6] or Lewis acid catalyzed tandem reactions.[7]

The development of efficient transition metal-catalyzed C–C and C-heteroatom bond-forming reactions is a central subject in current organic synthesis.[8] In line with the renewed interest for γ-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.

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Chao Shu was born in 1988 in Anhui, China. He received his BS degree from Anhui Normal University in 2011. He is currently a third year graduate student with Prof. Long-Wu Ye at Xiamen University. His current research interests focus on transition metal catalyzed synthesis of heterocycles.

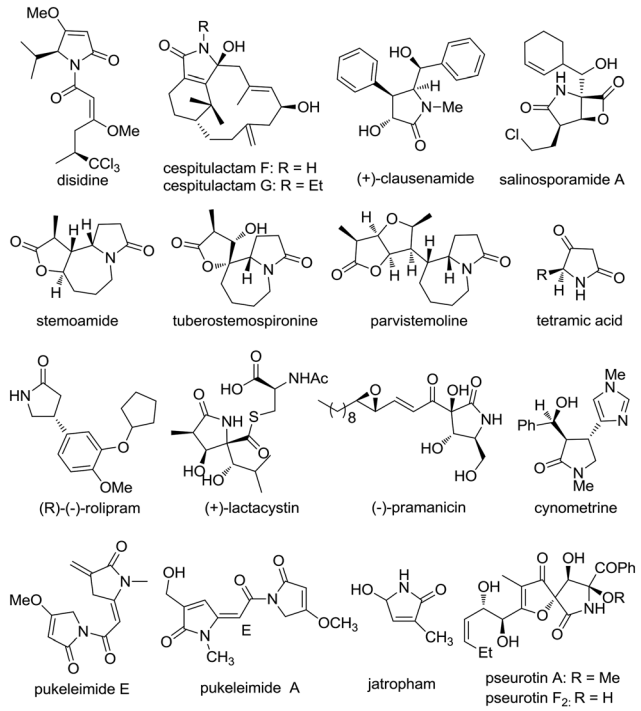


Fig. 1 Selected examples of naturally occurring γ-lactams.

As a very limited number of reviews have been published on this topic;[9] 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 γ-lactams. It should be pointed out that this review is strictly limited to the synthesis of this motif and that other 5-membered cyclic amides, such as oxindoles and phthalimidines, are not discussed herein.

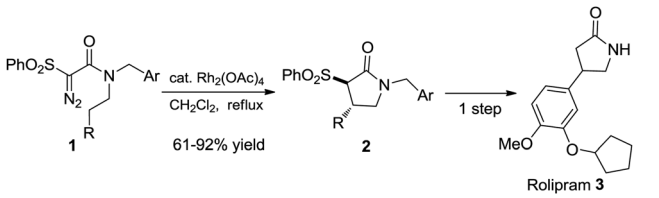
2. Rhodium catalysis

2.1. Rh-catalyzed intramolecular carbenoid C–H insertion

Since Doyle's pioneering work in the late 1980s,[10] the rhodium-catalyzed intramolecular C–H insertion reaction of

Fabien Gagosz

Fabien Gagosz obtained his Ph.D. with Prof. Samir Z. Zard at Ecole Polytechnique, France in 2002. After postdoctoral studies with Prof. William B. Motherwell at the University College, London, he returned to Ecole Polytechnique in 2004 to start his independent academic career as a Chargé de Recherche CNRS. He was promoted to Directeur de Recherche in 2012. His research concerns homogeneous catalysis in general, with a focus on late transition metal-catalyzed methods.



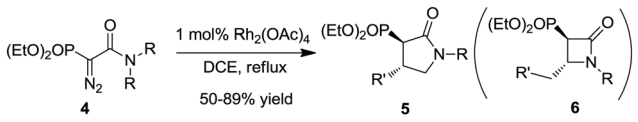
Scheme 1 Rh-catalyzed intramolecular C–H insertion of *N*-benzylated α-diazo-α-(phenylsulfonyl)acetamides **1**.

α-diazoamides has emerged as one of the most attractive methods for the synthesis of a variety of γ-lactams. While being of general interest, this approach often suffers from competitive reactions which result in the formation of regioisomers, including β- and γ-lactams, and/or stereoisomers. The ratio of products mainly depends on the nature of the substrates employed and the nature of ligands present in the rhodium complex used as a catalyst. In particular, it was found that the nature of the substituent at position α to the carbenoid carbon could significantly affect the chemoselectivity and regioselectivity of the C–H insertion reaction, as originally reported by Wee and Padwa.[11]

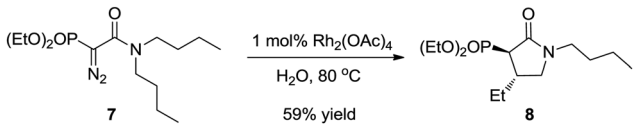
In a series of elegant studies, Jung and co-workers recently demonstrated that the presence of a phenylsulfonyl moiety at the α position of the carbenoid carbon could allow the regio- and the stereoselective Rh-catalyzed formation of highly functionalized γ-lactams.[12] In this case, the phenylsulfonyl group was proposed not only to alter the electron density at the carbenoid center but also to exert a steric effect during the C–H insertion reaction, thus explaining the high regioselectivity observed. In 2003, these authors reported the preparation of various γ-lactams **2** *via* a Rh-catalyzed cyclization of *N*-benzylated α-diazo-α-(phenylsulfonyl) acetamides **1**.[13] It was found that the reaction could afford *trans* γ-lactams **2** as the major products in moderate to excellent yields with a high regioselectivity (Scheme 1). It should be mentioned that in this case, besides the phenylsulfonyl group, the *N*-benzyl moiety also appears to enhance the regioselectivity of the C–H insertion. The interest of this method was further demonstrated by the total synthesis of rolipram **3**,[14] a known selective inhibitor of phosphodiesterase (PDE) type IV possessing anti-inflammatory and antidepressant activities.

Besides the phenylsulfonyl group, Afonso and co-workers found that a phosphoryl group could also be used to achieve high regioselectivity in Rh-catalyzed intramolecular C–H activation. In the presence of 1 mol% $Rh_2(OAc)_4$, the reaction of α-diazo-α-(dialkoxyphosphoryl)acetamides **4** indeed furnished the corresponding γ-lactams **5** in moderate to good yields with good stereocontrol of the *trans* diastereoselectivity (Scheme 2).[15] Importantly, the introduction of the bulky dialkoxyphosphoryl group significantly suppressed the formation of β-lactam **6**.

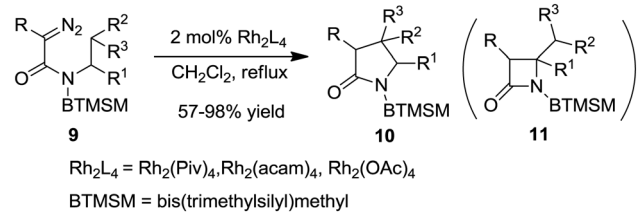
Additional studies showed that such an intramolecular C–H insertion reaction could proceed well even in neat water. For example, γ-lactam **8** could be readily obtained in water at 80 °C



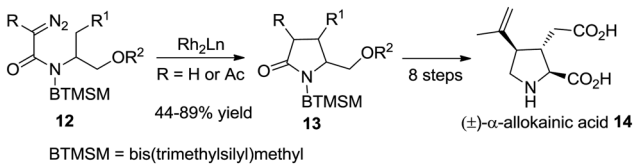
Scheme 2 Synthesis of α-phosphory-γ-lactams **5** *via* Rh-catalyzed cyclization of α-diazo-α-(dialkoxyphosphoryl)acetamides **4**.



Scheme 3 Synthesis of γ-lactam **8** *via* rhodium-catalyzed intramolecular C–H insertion.



Scheme 4 Synthesis of *N*-BTMSM protected γ-lactams **10** *via* Rh(II)-catalyzed C–H insertion reaction.

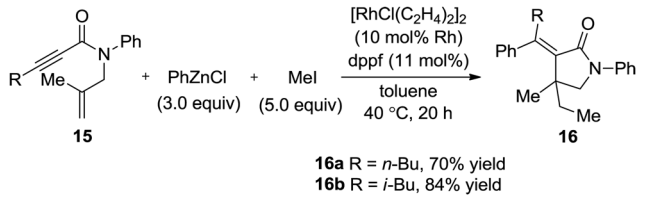


Scheme 5 Rh(II)-carbenoid-mediated synthesis of γ-lactams **13** from *N*-BTMSM diazoamides **12**.

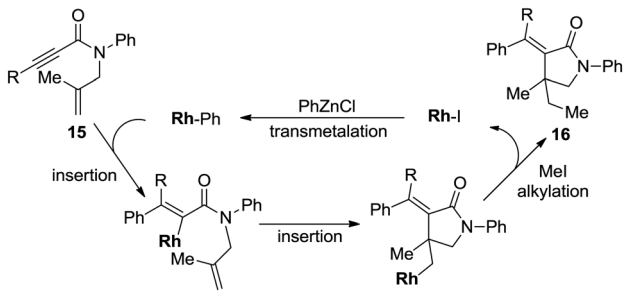
from α-diazo-α-phosphoryl-acetamide **7**, thus highlighting the practicability of this methodology (Scheme 3).[16]

In 2005, Wee and co-workers reported a Rh-catalyzed cyclization reaction to prepare *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) γ-lactams **10**. It was found that upon treatment with a Rh(II) catalyst, diazoamides **9** could be converted into the corresponding γ-lactams **10** in moderate to good yields (Scheme 4).[17] 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 **9**.

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 γ-lactams **13** with good to excellent regio-, chemo-, and diastereoselectivities.[18] 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



Scheme 6 Synthesis of γ-lactams **16** *via* rhodium-catalyzed multi-component-coupling reaction.



Scheme 7 Plausible catalytic cycle for the rhodium-catalyzed synthesis of γ-lactams **16**.

effect exerted by the OR^2 group. It was also proposed that the choice of the rhodium catalyst was crucial to perform effective control of the product distribution. The synthetic utility of this methodology was highlighted by the total synthesis of (±)-α-allokainic acid **14**.[19]

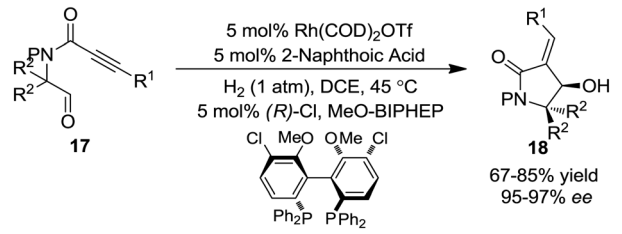
2.2. Rh-catalyzed multicomponent-coupling reaction

Rhodium-catalyzed multicomponent-coupling reactions have been employed as a mild and efficient way to generate new carbon–carbon bonds.[20] Application of this strategy to the preparation of functionalized γ-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 γ-lactams **16** in good yields (Scheme 6).[21]

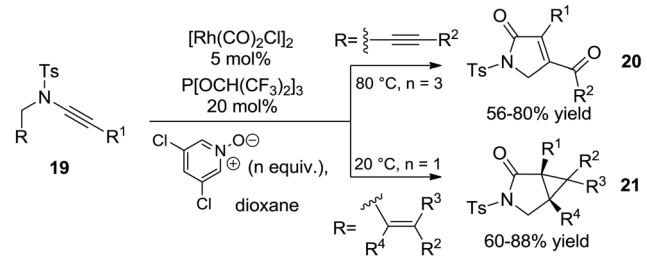
The reaction presumably proceeds following a two-step carborhodation–alkylation–transmetalation sequence, as shown in Scheme 7.[21]

2.3. Rh-catalyzed reductive cyclization of acetylenic aldehydes

Transition metal-catalyzed reductive coupling of alkynes with aldehydes has received considerable attention during recent years, as it represents a powerful and efficient way to generate new C–C bonds.[22] In 2006, Krische and co-workers reported that such a type of transformation could be used to produce γ-lactams in an enantioselective manner (Scheme 8). It was indeed found that the reductive cyclization of acetylenic aldehydes **17** into functionalized γ-lactams **18** could be efficiently performed in the presence of a rhodium catalyst under an atmosphere of hydrogen. Moderate to good yields and



Scheme 8 Synthesis of chiral γ-lactams **18** *via* rhodium-catalyzed asymmetric hydrogenation.



Scheme 9 Synthesis of γ-lactam derivatives **20** and **21** *via* a Rh-catalyzed oxidative cyclization.

excellent enantioselectivities were obtained when (*R*)-Cl, MeO-BIPHEP was used as the ligand.[23] Deuterium labelling studies revealed that the reaction might proceed *via* an oxidative coupling, followed by a hydrogenolytic cleavage of the resulting metallacycle involving a σ bond metathesis.

2.4. Rh-catalyzed oxidative cyclization of diynes and enynes

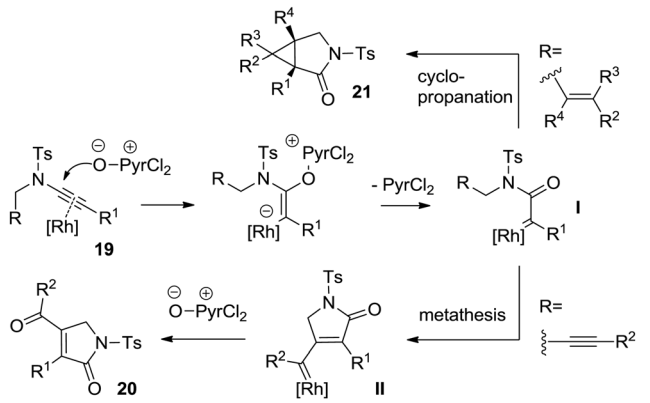
Very recently, Tang and co-workers have shown that a Rh(I) catalyst could be used in combination with a pyridine oxide to transform *N*-tosylamide derivatives **19** into unsaturated or cyclopropane ring fused γ-lactams of types **20** and **21** (Scheme 9). This oxidative cyclization proved to be efficient (56–88%) and allows rapid and practical access to a variety of functionalized γ-lactam derivatives under mild oxidative conditions.[24] 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, generates the key rhodium carbenoid **I**. Interaction of the 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**.

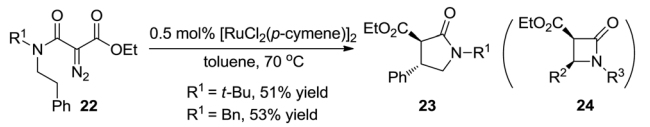
3. Ruthenium catalysis

3.1. Ru-catalyzed intramolecular carbenoid C–H insertion

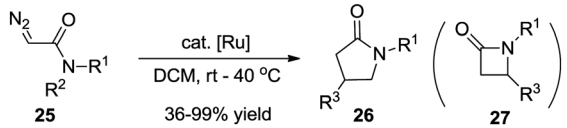
Although extensive efforts have been directed towards the development of metal-catalyzed γ-lactams synthesis by



Scheme 10 Proposed mechanism for the Rh(I)-catalyzed formation of γ-lactams **20** and **21**.



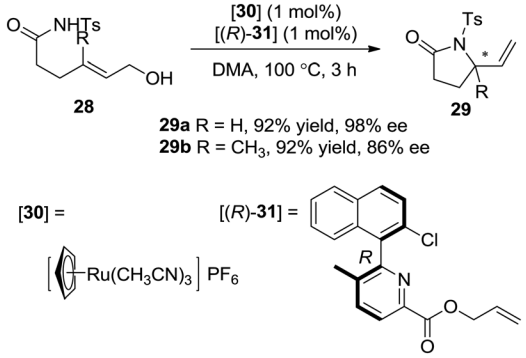
Scheme 11 Ruthenium-catalyzed intramolecular C–H insertion of α-diazoanilides **22**.



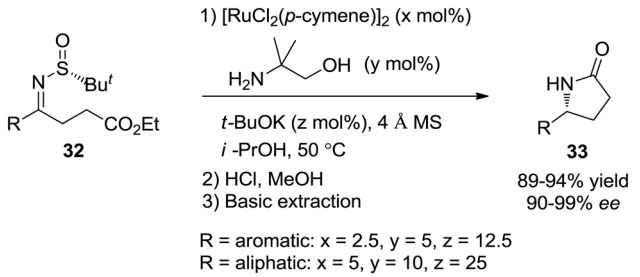
Scheme 12 Synthesis of γ-lactams **26** *via* ruthenium-catalyzed intramolecular C–H bond insertion.

intramolecular carbenoid C–H insertion reactions using α-diazocarbonyl substrates, relatively little work has been carried out regarding the possibility of using other metals than rhodium in such transformations. In 2005, Yu and co-workers reported that α-diazoacetamides **22** could undergo a smooth cyclization to give the corresponding γ-lactams **23** in serviceable yields albeit with minor *cis*-β-lactams **24** (Scheme 11).[25] Notably, this Ru-catalyzed reaction, which corresponds to an intramolecular carbenoid insertion into the aromatic C–H bond, required neither a slow addition of the diazo compound nor the use of an inert atmosphere.

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 the type $[Ru_2(CO)_4(\mu\text{-}L1)_2L_{22}]$ as the catalysts, they found that *N*,*N*-dialkyldiazoacetamides **25** could be converted into γ-lactams **26** in moderate to excellent yields (Scheme 12).[26] While being generally selective, this C–H bond insertion reaction also furnished in some cases β-lactams **27** as minor products.



Scheme 13 CpRu-catalyzed asymmetric synthesis of α-alkenyl γ-lactams **29**.



Scheme 14 Synthesis of γ-lactams **33** by asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)iminoesters **32**.

3.2. Ru-catalyzed dehydrative intramolecular *N*-allylation

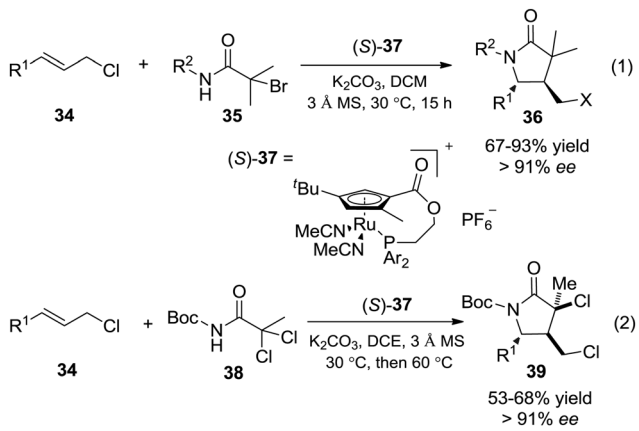
Recently, Kitamura *et al.* found that a combination of [CpRu-$(CH_3CN)_3$]PF_6 (**30**) with the chiral ligand Cl–Naph–Py–COOAll (**31**, All: allyl) was a suitable catalytic system for the intramolecular dehydrative *N*-allylation of *N*-Ts-protected ω-aminocarbonyl allylic alcohols **28**. The corresponding chiral α-alkenyl γ-lactams **29** were produced in excellent yields and good to excellent enantioselectivities (Scheme 13).[27]

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

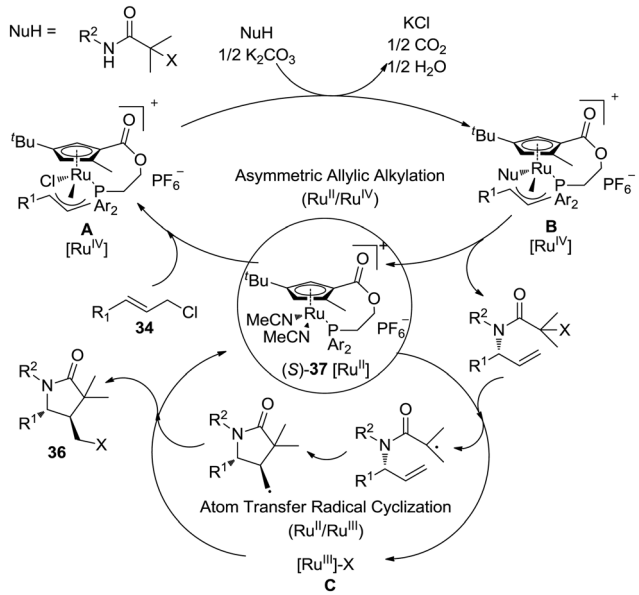
Very recently, Guijarro and co-workers reported a concise synthesis of chiral γ-lactam derivatives that involves a Ru-catalyzed asymmetric transfer hydrogenation reaction. Treatment of *N*-(*tert*-butylsulfinyl)iminoesters **32** with a ruthenium catalyst in the presence of 2-amino-2-methylpropan-1-ol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

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]



Scheme 15 Synthesis of chiral γ-lactams **36** and **39** by asymmetric auto-tandem catalysis.



Scheme 16 Proposed reaction mechanism of asymmetric auto-tandem catalysis.

It was found that the reaction of allylic chloride **34** with α-bromoamide **35** in the presence of planar-chiral CpRu 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 substrate. In this case, the reaction delivered the corresponding chiral γ-lactam derivatives **39** which possess three consecutive stereogenic centers in moderate yields (Scheme 15).

The reaction presumably involves an asymmetric auto-tandem catalysis, consisting of an asymmetric allylic substitution (Ru^{II}/Ru^{IV}) and a diastereoselective atom-transfer radical cyclization (ATRC, Ru^{II}/Ru^{III}), as depicted in Scheme 16.

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.

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 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 $PhI(OAc)_2$ in acetic acid, led to the isolation of γ-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 $PhI(OAc)_2$ provides the key $Pd^{(IV)}$ intermediate **III**. γ-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.

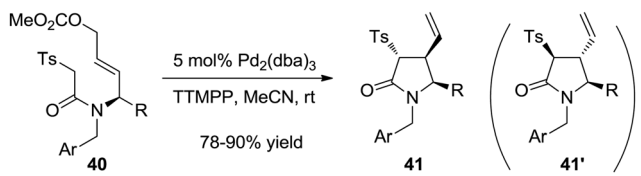
4.3. Pd-catalyzed allene carbopalladation/allylic alkylation reaction

In 2009, Prestat and Poli described a general route for the regio- and stereoselective synthesis of 4-(α-styryl) γ-lactams involving a phosphine-free Pd-catalyzed allene carbopalladation/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 γ-lactams **45** in moderate to good yields (61–88%).[32] This methodology was readily used in the facile synthesis of γ-lactam **46**, a racemic aza analogue of the naturally occurring lignan (+)-oxo-parabenzlactone **47**.

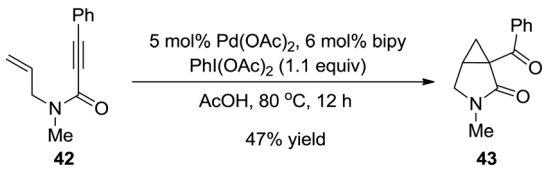
The mechanism shown in Scheme 21 was proposed to explain the formation of γ-lactam **45**. An initial oxidative addition of the aryl iodide onto $Pd^{(0)}$ generates the aryl palladium electrophilic species **I**, which then coordinates to the allene moiety of the substrate sodium salt **44**. A subsequent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

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

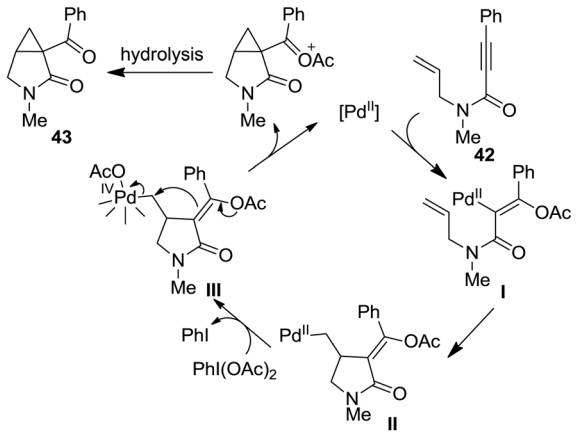
A palladium-catalyzed C–H olefination reaction has also been employed to construct γ-lactam derivatives (Scheme 22). In 2010, Yu and co-workers demonstrated that the reaction of CONHAr amides **48** with benzyl acrylate could afford the corresponding γ-lactams **50** in moderate to good yields.[33] The formation of **50** could be explained by an initial selective sp^3



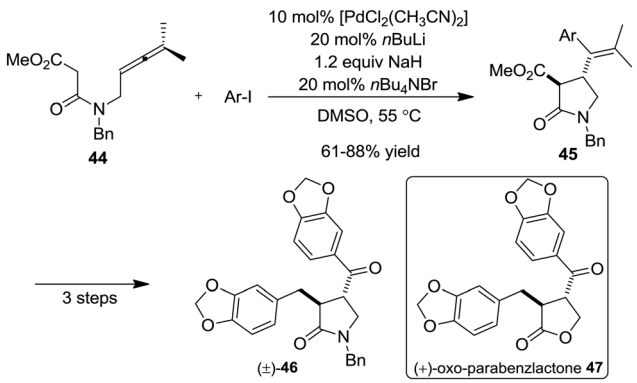
Scheme 17 Pd-catalyzed intramolecular allylation for the construction of polysubstituted γ-lactam carbonates **41**.



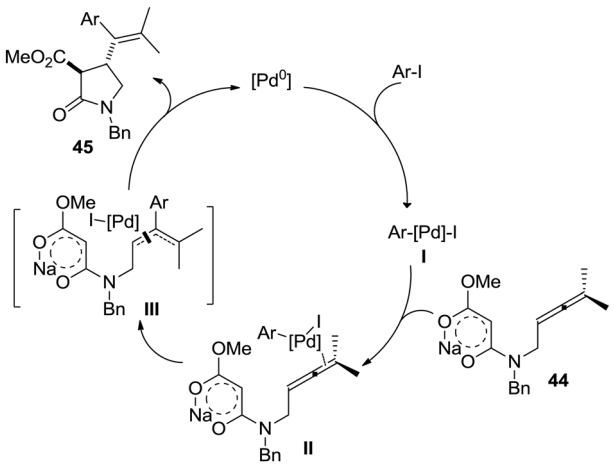
Scheme 18 Synthesis of fused γ-lactam **43** through Pd-catalyzed reaction of enyne **42**.



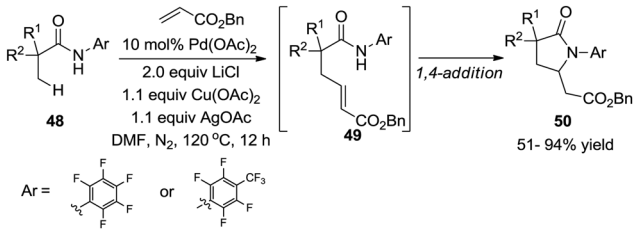
Scheme 19 Plausible mechanism for the Pd(II)-catalyzed oxidation reaction.



Scheme 20 Synthesis of γ-lactams **45** *via* carbopalladation/allylic alkylation domino sequence.



Scheme 21 Proposed mechanism for the Pd-catalyzed allene carbopalladation/allylic alkylation reaction.

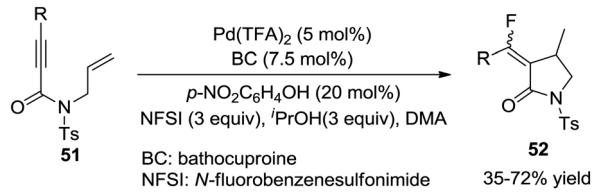


Scheme 22 Synthesis of γ-lactams **50** *via* Pd-catalyzed olefination of sp^3 C–H bonds.

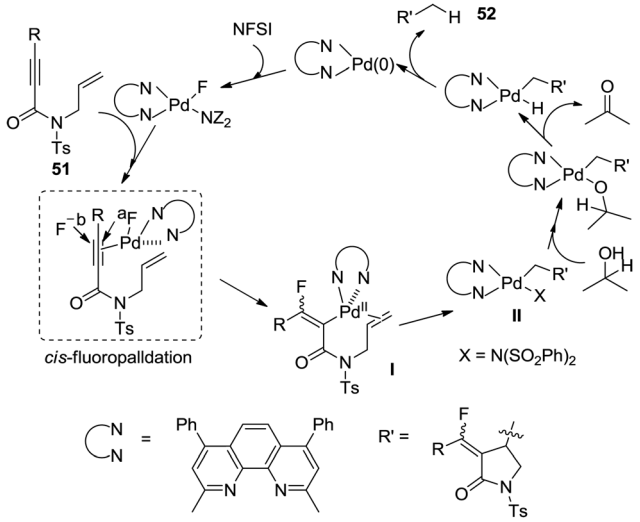
C–H activation producing intermediate **49**, which undergoes a subsequent intramolecular 1,4-conjugate addition.

4.5. Pd-catalyzed tandem fluorination and cyclization of enynes

Recently, a novel and direct route for the synthesis of fluorinated γ-lactams by a Pd-catalyzed tandem alkyne fluorination/enyne cyclization has been reported by Liu and co-workers. Treatment of enyne **51** with $Pd(TFA)_2$ (5 mol%), bathocuproine (7.5 mol%), 4-nitrophenol (20 mol%) and excess of NFSI and i-PrOH in DMA afforded the γ-lactams **52** in moderate to good yields (Scheme 23).[34] This procedure represents a useful entry to fluorinated γ-lactams from readily accessible 1,6-enynes. 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**.



Scheme 23 Pd-catalyzed synthesis of fluorinated γ-lactams **52**.



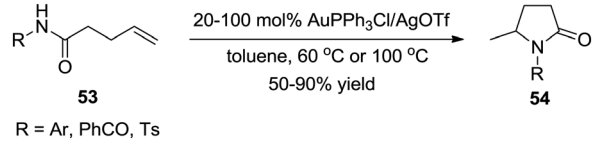
Scheme 24 Plausible mechanism for the Pd-catalyzed synthesis of fluorinated γ-lactams **52**.

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 **I**. The latter undergoes an intramolecular alkene insertion to produce a new intermediate **II**, which is then reduced in the presence of i-PrOH to finally deliver the fluorinated γ-lactam **52**.

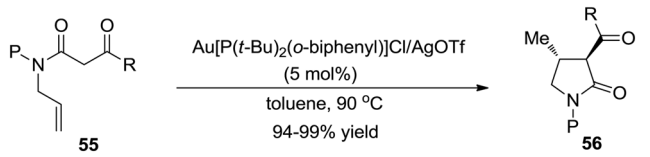
5. Gold catalysis

5.1. Au-catalyzed hydroamination of alkenes

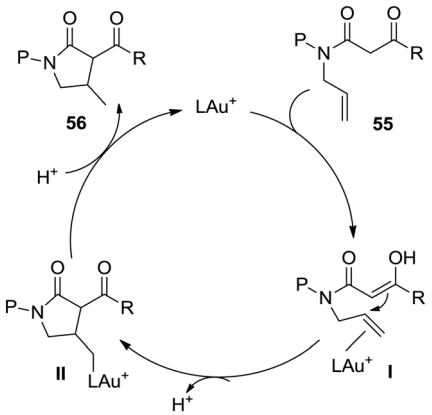
In the last decade, homogeneous gold catalysis has proven to be a powerful tool in organic synthesis, leading to the formation of an incredible variety of different heterocyclic motifs.[35] The application of gold catalysis to the construction of the versatile γ-lactam motif was recently investigated. 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% $Ph_3PAuOTf$ in toluene produced the corresponding γ-lactams **54** in moderate yields.[36] Notably, excellent yields could be achieved by employing a stoichiometric amount of $Ph_3PAuOTf$.



Scheme 25 Synthesis of γ-lactams **54** through gold-catalyzed hydroamination of alkenes **53**.



Scheme 26 Synthesis of γ-lactams **56** *via* an intramolecular addition of β-ketoamide to unactivated alkenes **55**.



Scheme 27 Mechanistic proposal for the gold-catalyzed synthesis of γ-lactams **56**.

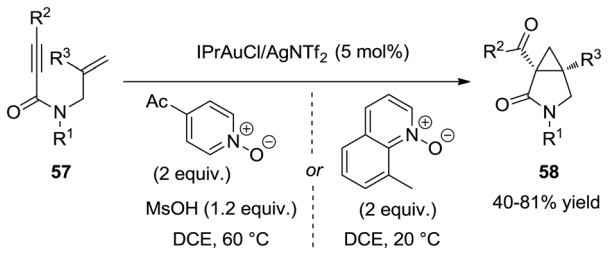
5.2. Au-catalyzed intramolecular addition of β-ketoamide to unactivated alkenes

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 alkenes (Scheme 26).[37] It was found that in the presence of 5 mol% of the Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf catalytic system, β-ketoamides **55** could be cyclized into the highly substituted γ-lactams **56** in excellent yields. Interestingly, the reaction can be performed in aqueous media and is amenable to the large-scale preparation of γ-lactams. This transformation is the first reported one to show the potential of gold to catalyze the intramolecular addition of 1,3-dicarbonyl moiety onto unactivated alkenes.

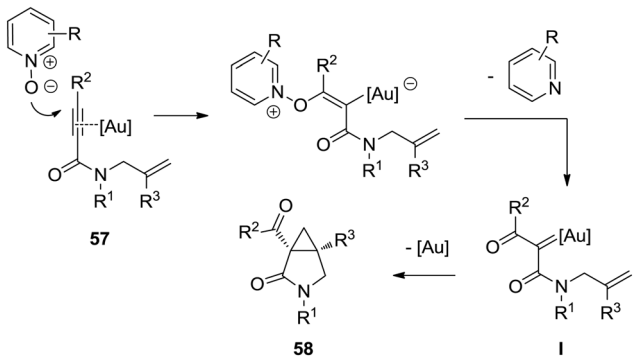
The mechanism of this interesting process is shown in Scheme 27. The cationic $gold^{(I)}$ complex first coordinates to substrate **55** to produce the alkene gold-(I) complex **I**. A 5-*exo*-trig addition of the enol form of the β-ketoamide subsequently gives intermediate **II**, which is proto-demetalated to finally afford γ-lactam **56** with regeneration of the gold catalyst.

5.3. Au-catalyzed oxidation-cyclopropanation sequence of enynes

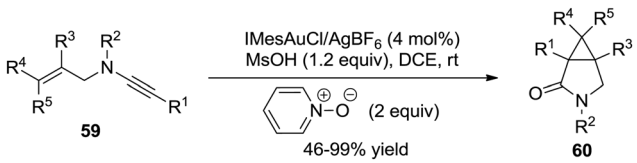
In 2011, Zhang and Qian reported an interesting oxidative cyclization of 1,6-enynes of type **57** in the presence of a $gold^{(I)}$ catalyst and a pyridine oxide (Scheme 28).[38] It is noteworthy that this transformation is efficient and leads to cyclopropane fused γ-lactams **58** which share noticeable structural



Scheme 28 Synthesis of cyclopropane fused γ-lactams **58** *via* an oxidative cyclization of 1,6-enynes **57**.



Scheme 29 Mechanism for the gold-catalyzed oxidative cyclization of 1,6-enynes **57**.



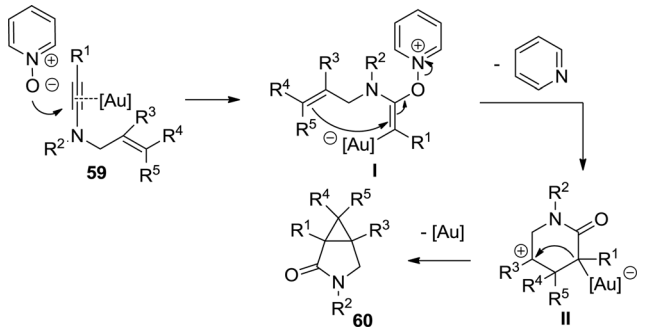
Scheme 30 Synthesis of cyclopropane fused γ-lactams **60** *via* an oxidative cyclization of 1,5-enynes **59**.

similarities with those which can be obtained under Rh or Pd catalysis (see sections 2.4 and 4.2).

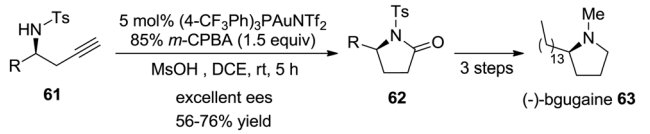
The formation of γ-lactams **58** was explained by the interception of a postulated gold carbenoid **I** by the pendant alkene chain (Scheme 29). Reactive intermediate **I** is supposed to be generated after a gold-catalyzed pyridine oxide addition onto the alkyne in **57** followed by elimination of 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).[39] 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*-allylynamides **59** to generate vinyl gold intermediate **I**. Subsequent intramolecular nucleophilic addition of an alkenyl moiety and loss of



Scheme 31 Proposed mechanism of the gold-catalyzed oxidative cyclization of *N*-allylynamides **59**.



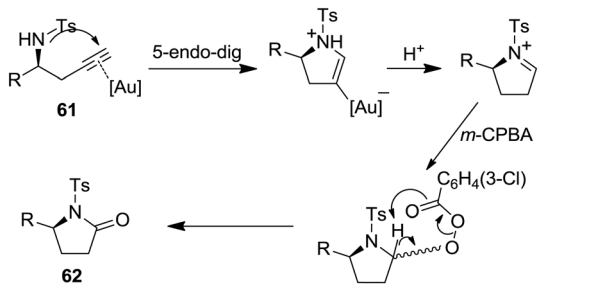
Scheme 32 Gold-catalyzed synthesis of γ-lactams **62** from homopropargyl amides **61**.

pyridine allow the formation of intermediate **II**, which can be further transformed into the final product **60**, and regenerate the gold catalyst.

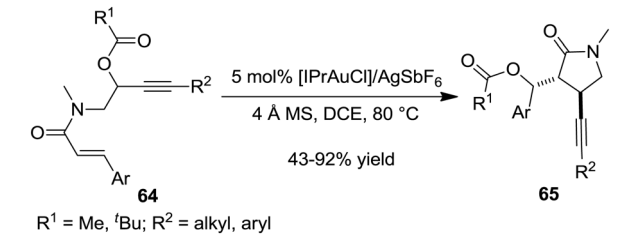
5.4. Au-catalyzed tandem cycloisomerization/oxidation of homopropargyl amides

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 (−)-bgugaine **63**.

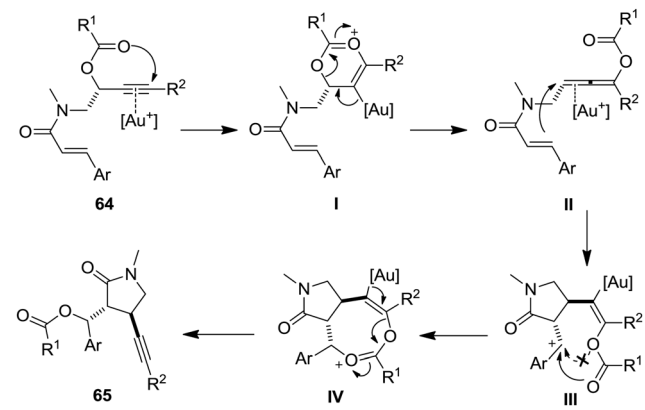
The formation of γ-lactams **62** could be explained by a gold-catalyzed oxycyclization producing vinyl gold intermediate, followed by an acid-accelerated oxidation (Scheme 33).



Scheme 33 Plausible mechanism for the gold-catalyzed synthesis of γ-lactams **62**.



Scheme 34 Synthesis of γ-lactams **65** *via* gold-catalyzed formal 1,6-acyloxy migration of propargylic esters **64**.



Scheme 35 Mechanistic proposal for the gold-catalyzed synthesis of γ-lactams **65**.

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

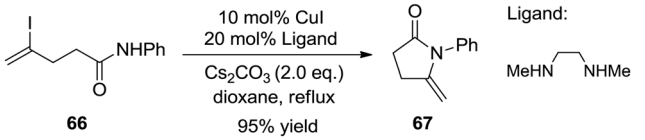
Very recently, Hashmi and co-workers reported an unprecedented route based on a gold-catalyzed formal 1,6-acyloxy migration of propargylic esters for the synthesis of 3,4-disubstituted γ-lactams (Scheme 34).[41] It was indeed found that in the presence of 5 mol% of the [IPrAuCl]/$AgSbF_6$ catalytic system, 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 a similar gold-catalyzed formal 1,6-phosphatyloxy migration and 1,6-carbonate migration.[42]

The mechanism shown in Scheme 35 has been proposed to explain this gold-catalyzed formal 1,6-acyloxy migration reaction. A gold-catalyzed [3,3]-sigmatropic rearrangement allows the initial formation of the allene–gold complex intermediate **II**, which undergoes a subsequent nucleophilic attack of the olefin to generate intermediate **III**. A final 1,5-migration of the acyloxy group *via* an eight-membered cyclic intermediate **IV** furnishes the γ-lactam product **65**. This mechanism and especially the involvement of intermediate **IV** were supported by DFT computational studies.

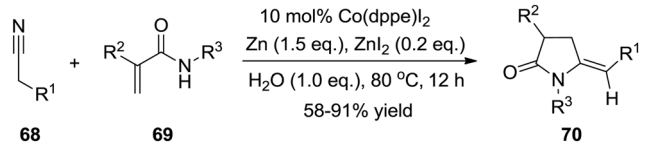
6. Copper catalysis

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,



Scheme 36 Synthesis of *N*-vinylic γ-lactam **67** *via* copper-catalyzed intramolecular coupling of iodoenamide **66**.



Scheme 37 Synthesis of γ-lactams **70** *via* Co-catalyzed reductive coupling of nitriles **68** with acrylamides **69**.

with iodoalkenes to produce *N*-alkenyl lactams in moderate to excellent yields. For example, treatment of 4-iodo-*N*-phenyl-pent-4-enamide **66** with a catalytic amount of CuI (10 mol%) and *N*,*N*′-dimethylethylenediamine (20 mol%) led to the formation of the *N*-vinylic 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

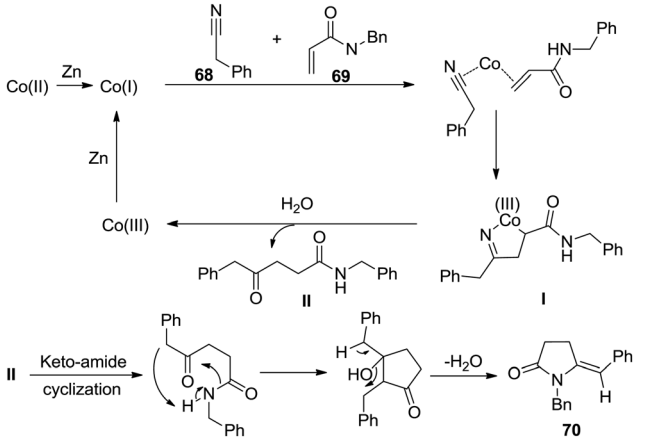
During the last decade, a lot of attention has been paid to the development of metal-catalyzed regioselective reductive coupling (RRC). Indeed, this type of transformation allows the synthesis of highly functionalized products in a generally step- and atom-economical manner.[44] In 2009, Cheng and co-workers disclosed a new type of Co-catalyzed reductive coupling for the preparation of γ-lactams. They discovered that the reaction of nitriles **68** with a variety of acrylamides **69** in the presence of 10 mol% of Co(dppe)I_2 and zinc could produce γ-lactams **70** in moderate to excellent yields (Scheme 37).[45]

A proposed mechanism for the formation of lactams **70** 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 **68** and acrylamide **69** 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**.

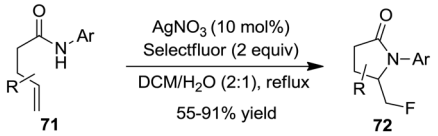
8. Silver catalysis

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



Scheme 38 Mechanistic proposal for the reaction of nitriles **68** with acrylamides **69**.



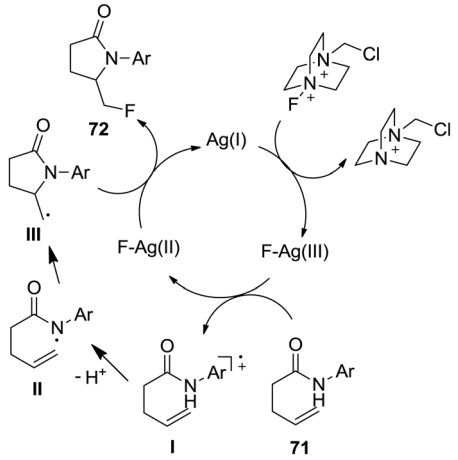
Scheme 39 Synthesis of fluoro γ-lactams **72** *via* Ag-catalyzed radical aminofluorination of unactivated alkenes **71**.

aminofluorination reaction. It was found that the fluoro γ-lactams **72** could be synthesized under mild reaction conditions by an intramolecular cyclization of unactivated amidoalkenes **71**.[46] Various fluoro γ-lactams were isolated in fairly good yields by reacting **71** with 5 mol% of $AgNO_3$ and 10 mol% of Selectfluor®, in a mixture of dichloromethane and water (Scheme 39). It should be pointed out that Selectfluor® served both as the fluorine source and the oxidant in this transformation.

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 **72** (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 metals, 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 for the substrate scope and



Scheme 40 Mechanistic proposal for the formation of fluoro γ-lactams **72**.

the functional group tolerance which should be extended, the nature of the catalytic systems which require more modularity and practicability, and the possibility of performing 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 academic and industrial chemists will be made in the next decades.

Acknowledgements

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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 310 000 hits.

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