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REVIEW

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Intramolecular cyclization of *N*-allyl propiolamides: a facile synthetic route to highly substituted γ-lactams (a review)

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The development of simple and efficient methods for construction of substituted γ-lactams is an important synthetic goal because such ring skeletons are present in numerous natural compounds that display diverse biological activities. Intramolecular cyclization of *N*-allyl propiolamides is an efficient, economic, and operationally simple strategy for the synthesis of the titled compounds. In the present review we will discuss recent advances in the synthesis of functionalized γ-lactam derivatives from these easily accessible and versatile building blocks with the emphasis on the mechanistic aspects of the reactions.

1. Introduction

Needless to say, γ-lactams are at the heart of a number of medicinally and biologically important compounds, as well as a large array of natural products. For instance, brivaracetam **1**, with the brand name Briviact, is an anticonvulsant drug marketed worldwide for the treatment of partial onset seizures.[1] Piracetam **2** (also known as a smart drug) is a nootropic supplement that has the ability to enhance memory and learning ability. It also used as an adjunctive treatment for myoclonus of cortical origin.[2] Marizomib **3** is a naturally-occurring salinosporamide, isolated from the marine actinomycete *Salinospora tropica*. This compound is a promising drug candidate for the treatment of multiple myeloma and mantle cell lymphoma.[3,4] Annosqualine **4**, which has good antibacterial activity, is a natural product isolated from the stems of *Annona Squamosa*.[5,6] Codinaeopsin **5**, which was isolated from an endophytic fungus collected in Costa Rica, has significant antimalarial activity.[7] This biological activity has made the synthesis of γ-lactams quite attractive, and a large number of straightforward and robust methods for the construction of these cores has been established.[8–12] More recently, Rivas and

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Ling published an interesting review paper that covers most of the recent advances in the synthesis of the titled compounds.[12] However, synthesis of these cores through intramolecular cyclization of simple and easily accessible *N*-allyl propiolamide derivatives was omitted, while this synthetic strategy has recently attracted much attention because of its high efficiency, atom economy, and operational simplicity (Fig. 1).

In connection with our series of review papers on the synthesis of nitrogen based heterocycles from *N*-propargylamine/amide derivatives,[13–22] we summarize here a variety of protocols for the synthesis of γ-lactam cores from readily accessible *N*-allyl propiolamides. The review is divided into two major sections. The first section focuses exclusively on transition metal-catalyzed cyclization of *N*-allyl propiolamides, while the second covers radical promoted cyclizations. It should be noted that we have not discussed synthesis of indolinones (benzene-fused γ-lactams), since it has recently been described in another publication.[13]

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2. Transition metal-catalyzed cyclizations

2.1 Palladium

Synthesis of γ-lactams *via* Pd-catalyzed intramolecular cyclization of propiolamide derivatives has been the subject of a number of papers. One of the earliest report on this chemistry have been published by Lu and co-workers in 1996. They showed that treatment of *N*-allyl propiolamides **6** with the $PdCl_2(PhCN)_2/CuCl_2/LiCl$ system in acetonitrile directly gave corresponding α-chloromethylene-β-chloromethyl-γ-lactams **7** after 6–40 hours at room temperature (Scheme 1). According to the author proposed mechanism, this transformation proceeded *via* a chloropalladation/oxidative cleavage/insertion sequential process.[23] In a closely related study, the same group found that *N*-(3′-formylallylic)propiolamides **8** were converted to the corresponding α-bromomethylene-β-formylmethyl-γ-lactams **9**, *via* Pd(II)-catalyzed intramolecular cyclization using LiBr as bromide source in HOAc at room temperature (Scheme 2).[24]

In 2005, Zhu and Zhang described the first $PdCl_2$-catalyzed *cis*-chloropalladation-cyclization reaction of *N*-allyl propiolamides. Thus, the treatment of 1,6-enyne substrates **10** with 5 mol% of $PdCl_2$ in HOAc at 50 °C afforded corresponding (*E*)-α-halomethylene-γ-lactams **11** in high isolated yields (Scheme 3a). The mechanism proposed for the formation of γ-lactams **11** involves the key intermediate **A**, which underwent dehalopalladation to produce the cyclized product.[25] Subsequently, the same authors extended this chemistry to synthesis of α-phenylmethylene-γ-lactams **13** *via* a beautiful Pd(0)-catalyzed tandem cyclization/Suzuki coupling reaction of *N*-allyl propiolamides **12** with phenylboronic acid.[26] Several catalysts, bases and solvents were tested, and the system $Pd(PPh_3)_4$/KF/toluene was found to be superior.[27] Under optimized conditions, the reaction tolerates both aryl and alkyl substituted internal propiolamides and gave the corresponding lactams **13** in high yields (Scheme 3b).

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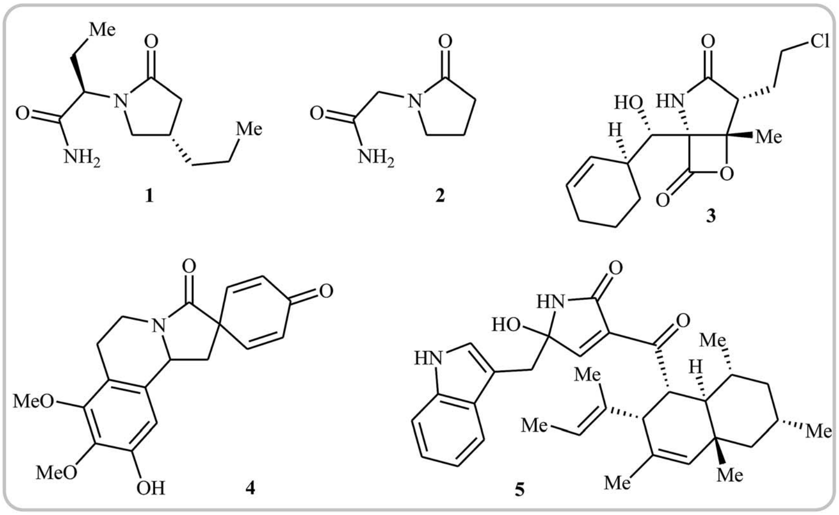
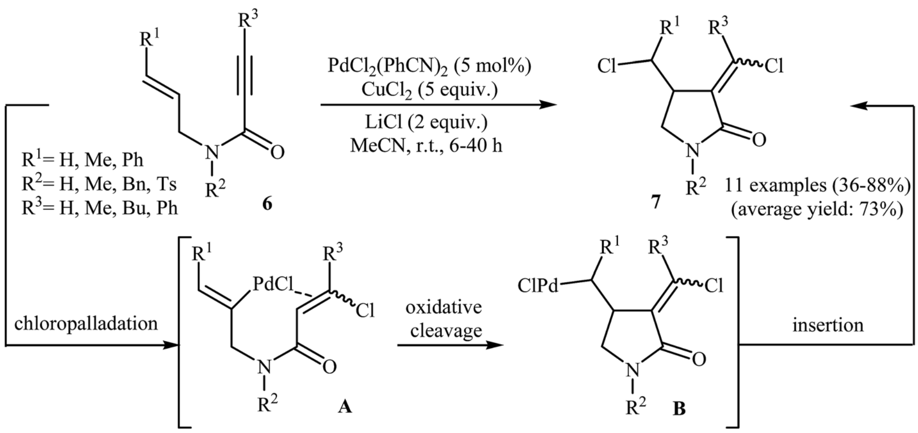
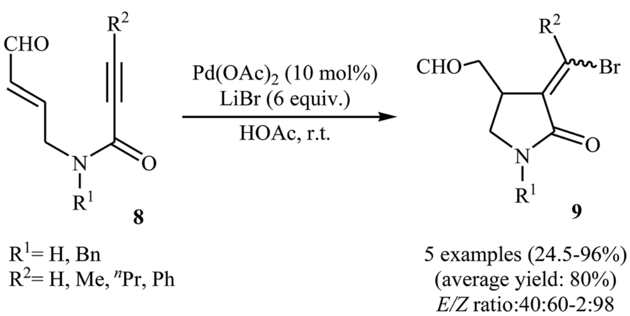


Fig. 1 Selected examples of bioactive γ-lactams.



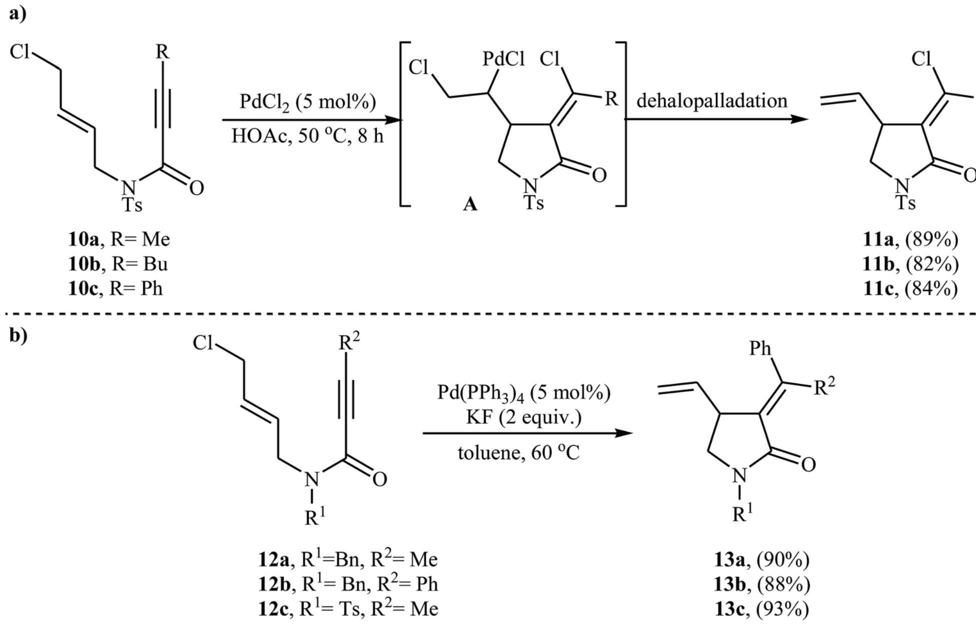
Scheme 1 Lu's synthesis of α-chloromethylene-β-chloromethyl-γ-lactams 7.



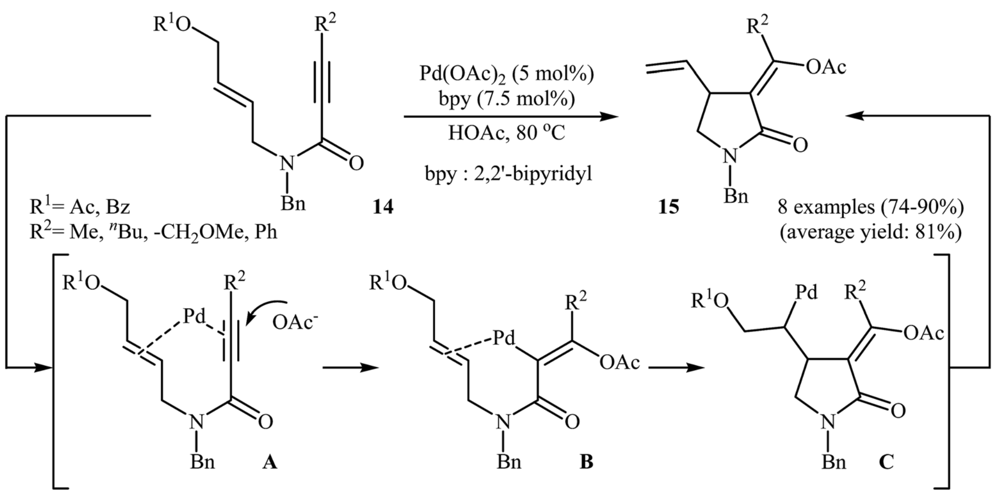
Scheme 2 Pd(II)-catalyzed cyclization of *N*-(3′-formylallylic)propiolamides 8 reported by Lu.

Shortly afterward, the group of Lu successfully synthesized a series of (*Z*)-α-alkylidene-γ-butyrolactams **15** from corresponding (*Z*)-*N*-allyl propiolamides **14** in good yields, as a single isomer, using 5 mol% of $Pa(OAc)_2$ as catalyst, and 7.5 mol% of bpy as ligand in acetic acid (Scheme 4). Mechanistically, the reaction proceeded *via* a coordination/intramolecular insertion/*trans*-acetoxypalladation/β-heteroatom elimination sequential process. The author found that when the reaction was carried out in the presence of chiral nitrogen-containing ligands, an asymmetric version of this protocol with moderate enantioselectivity was established.[28]

In 2010, the same group reported an elegant approach for the synthesis of α-alkylidene-β-hydroxy-γ-lactams **18** *via* Pd(II)-catalyzed cascade reaction of propiolamides **16** and arylboronic acids **17**. The optimum conditions for this reaction utilize $Pd(OAc)_2$ as the catalyst, bpy as ligand and DCE/H_2O (20 : 1) as solvent. Under optimized conditions, the reaction tolerates both terminal and alkyl substituted propiolamides and gave corresponding γ-lactams **18** in moderate to excellent yields, but extension of the reaction to aryl substituted alkynes and *N*-arylpropiolamides was failed (Scheme 5). The postulated reaction mechanism is displayed in Scheme 6. The reaction starts with *in situ* generation of bpyPd$(OAc)_2$ by reaction between the $Pd(OAc)_2$ and bpy. Its reaction with arylboronic acid **17** leads to an arylpalladium specie **A** that, after coordination with the triple bond and the carbonyl group of substrate **16**, affords



Scheme 3 (a) $PdCl_2$-catalyzed *cis*-chloropalladation-cyclization of *N*-allyl propiolamides **10**; (b) Pd(0)-catalyzed tandem cyclization/Suzuki coupling reaction of *N*-allyl propiolamides **12** with phenylboronic acid.

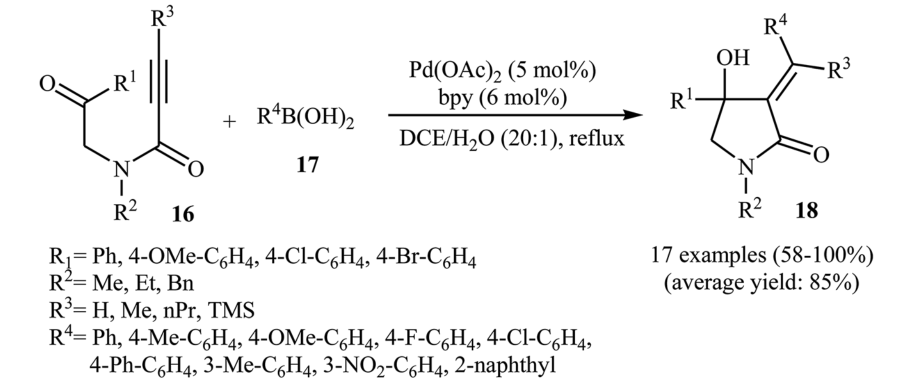


Scheme 4 Pd(II)-catalyzed asymmetric synthesis of (*Z*)-α-alkylidene-γ-butyrolactams **15** from corresponding (*Z*)-*N*-allyl propiolamides **14**.

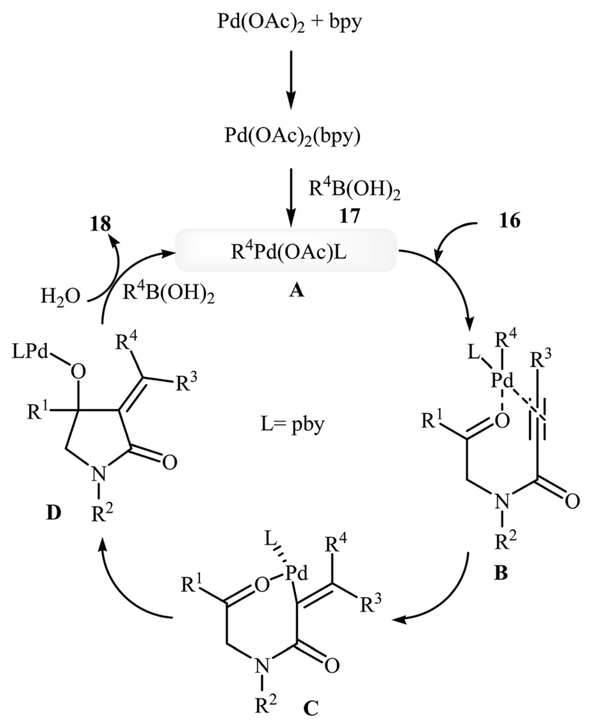
intermediate **B**. The insertion of the triple bond to arylpalladium species in **B** furnishes vinylpalladium intermediate **C**. Next, an intramolecular 1,2-addition of the vinylpalladium species to the carbonyl group in **C** takes place to form intermediate **D** which finally furnishes the final product **18** by a rapid protodemetalation and regeneration of the palladium(II) species.[29]

Inspired by these works, Peng and Liu reported a beautiful palladium(II)-catalyzed tandem fluorination and cyclization of *N*-allyl propiolamides **19** to prepare α-fluoromethylene γ-lactams **20**. It was found that upon treatment with *N*-fluorobenzenesulfonimide (NSFI) as fluorinating reagent, $Pd(TFA)_2$/BC as catalytic system and isopropyl alcohol and 4-nitrophenol as additives, *N*-allyl propiolamides **19** could be converted into the corresponding fluorinated γ-lactams **20** in moderate to good yields and high (*E*)-selectivity (Scheme 7). However, substrates bearing alkyl groups in the alkyne terminus failed to participate in the reaction. The results also demonstrated that the substrates with disubstituted alkene afforded only trace of γ-lactams.[30]

An interesting domino procedure for the synthesis of 3-azabicyclo[3.1.0]hexan-2-ones **22** from *N*-allyl propiolamides **21** through a 5-*exo*-trig cyclization and S_N2 C–O formation process, in which three new C–C bonds are formed, was developed by Tse and co-workers. The reaction was performed in the presence of $Pd(OAc)_2$/$PhI(OAc)_2$ combination as catalytic system in acetic acid and resulted in the formation of desired products **22** in good yields (Scheme 8a).[31] In a closely related investigation, the



Scheme 5 Synthesis of α-alkylidene-β-hydroxy-γ-lactams 3 *via* Pd(II)-catalyzed annulation of propiolamides **16** with arylboronic acids **17**.

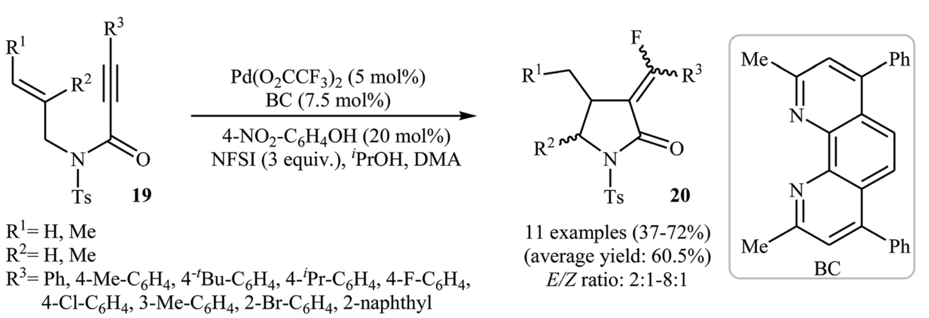


Scheme 6 Mechanism that accounts for the formation of **18**.

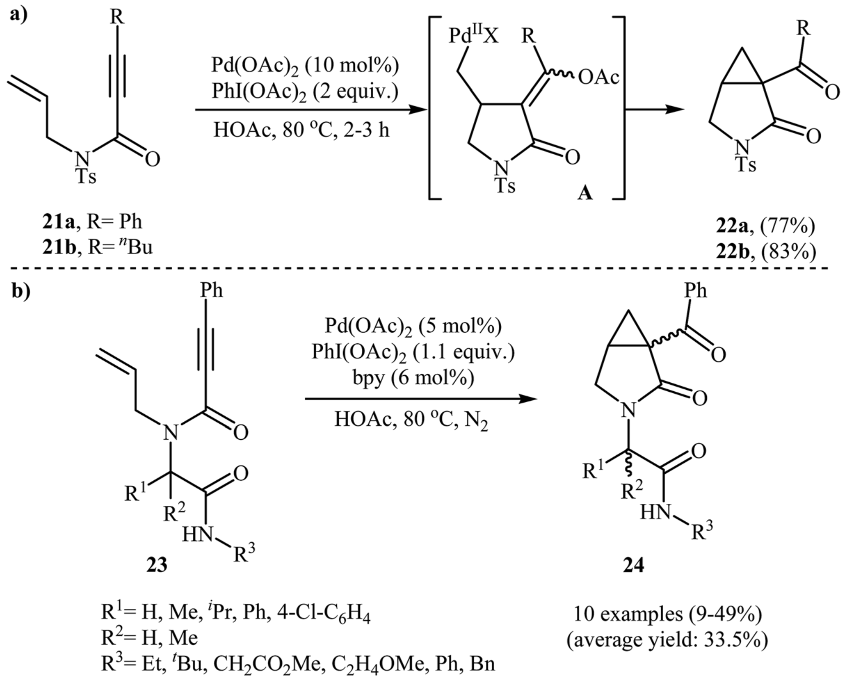
group of Welsch reported the cyclization of a series of Ugi-adducts **23** to construction of bicyclic lactams **24** employing $Pd(OAc)_2/PhI(OAc)_2$/bipy as catalytic system in HOAc. The 3-aza-bicyclo[3.1.0]hexan-2-ones **24** were formed with low to moderate yields (Scheme 8b). Unexpectedly, the authors did not notice any yield improvement when microwave irradiation was applied.[32]

2.2 Rhodium

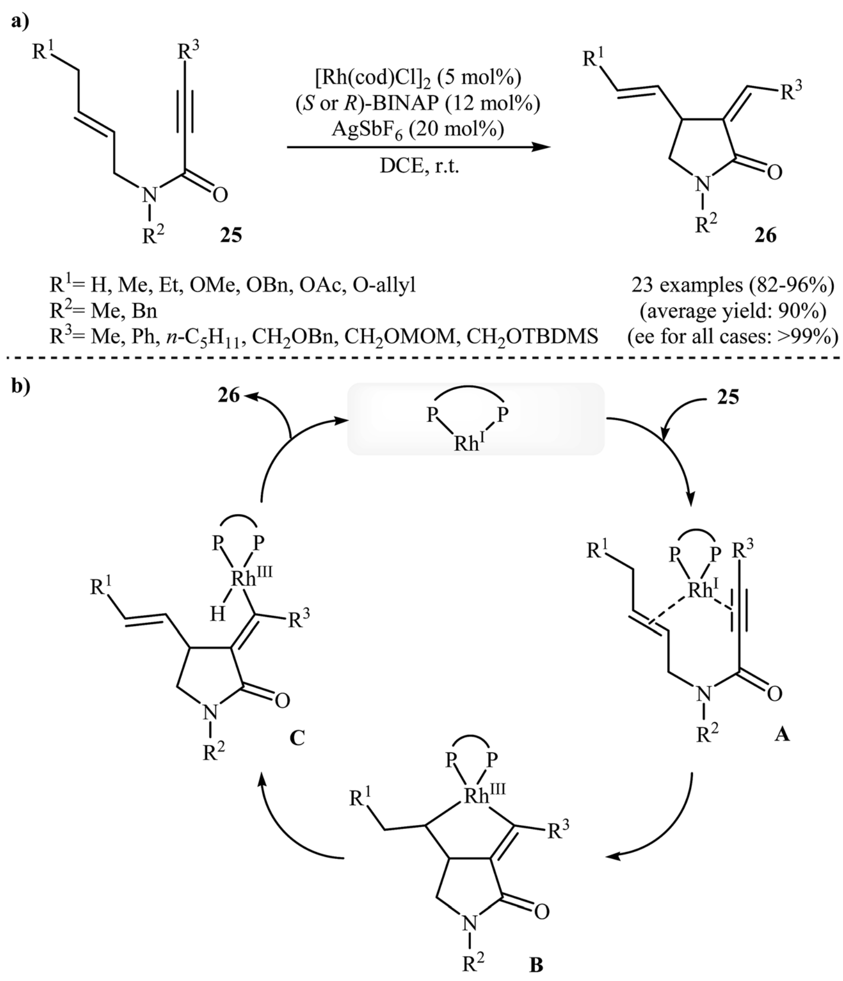
In 2002, the group of Zhang have shown that a commercially available Rh(I) catalyst $[Rh(cod)Cl]_2$ could be used in combination with BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) and $AgSbF_6$ to transform *N*-allyl propiolamides **25** into functionalized γ-lactams **26** (Scheme 9a). This enantioselective cycloisomerization proved to be highly efficient (82–96%) and allows general and practical access to a variety of functionalized γ-lactams under very mild reaction conditions. The excellent ee value (up to 99%) obtained in these reactions was especially remarkable. These results are consistent with a mechanism proceeding by the coordination of *N*-allyl propiolamides **25** with a RhI species to form intermediate **A**, followed by an intramolecular oxidative cyclization to form metallacyclopentane **B.** The Rh–H species **C** would be formed *via* β-H elimination of the metallacyclopentane **B.** The reductive elimination of this Rh–H species **C** would then give products **26** and generate RhI species (Scheme 9b).[33] Interestingly, when *N*-allyl propiolamides **27** having a halogen on the allylic terminus were subjected to cyclizations, another type of Rh(I)-catalyzed ene reaction was observed. In these cases an unusual intramolecular halogen shift happened to give α-halomethylene-γ-butyrolactones **28** as product (Scheme 10).[34–36]



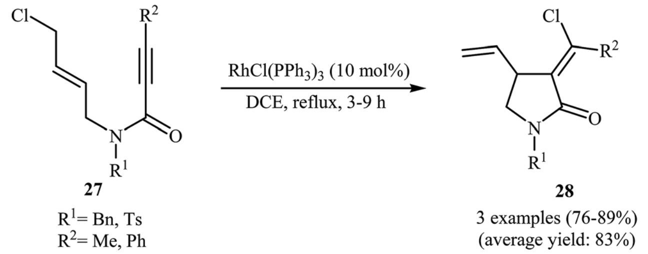
Scheme 7 Pd(II)-catalyzed tandem fluorination and cyclization of *N*-allyl propiolamides **19** developed by Liu.



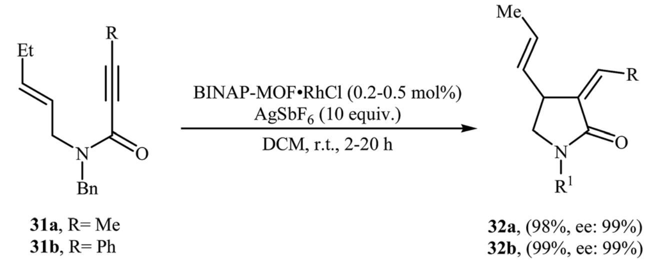
Scheme 8 (a) Tse's synthesis of 3-aza-bicyclo[3.1.0]hexan-2-ones **22**; (b) synthesis of bicyclic lactams **24** from Ugi-adducts **23**.



Scheme 9 (a) Enantioselective Rh-catalyzed cycloisomerization of propiolamides **25** into γ-actams **26**; (b) plausible mechanism for the formation of **26**.



Scheme 10 Rh(II)-catalyzed cycloisomerization of *N*-allyl propiolamides **27** with an intramolecular halogen shift.



Scheme 12 Lin's synthesis of γ-lactams **32**.

In 2012, Zhang and Ratovelomanana-Vidal along with their co-workers were able to demonstrate that a cationic Rh–Synphos catalyst can efficiency catalyze the cycloisomerization of *N*-allyl propiolamides **29** with an intramolecular halogen shift to the corresponding enantiomerically enriched α-chloromethylene-γ-butyrolactams **30** in moderate to high yields and good to very high enantiomeric excesses (Scheme 11). The reaction showed good functional group tolerance and could be applied for synthesis of various functionalized γ-lactams with potential biological activities.[37]

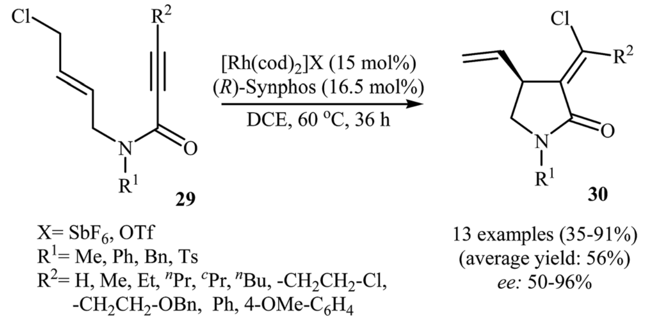
Recently, Lin and co-workers have described the synthesis of BINAP-based metal–organic framework BINAP–MOF (formula $Zr_6(OH)_4O_4(\mathbf{L1})_6$) *via* a solvothermal reaction between 4,4′-bis(4-carboxyphenylethynyl)BINAP ($H_2\mathbf{L1}$), $ZrCl_4$, and trifluoroacetic acid in DMF, which can be metalated with rhodium complex $[Rh(nbd)Cl]_2$ to provide highly active and enantioselective single-site catalyst BINAP–MOF RhCl for the asymmetric Alder-ene cycloisomerization reactions of *N*-allyl propiolamides **31** to provide the corresponding γ-lactams **32** in excellent yields and outstanding enantioselectivity (Scheme 12).[38]

2.3 Gold

In 2009, the group of Kang and Chung demonstrated for the first time the usefulness of gold catalysts for the cycloisomerization reaction of *N*-allyl propiolamides. Thus, in the presence of 5 mol% of $[Au(PPh_3)]SbF_6$ in dichloromethane at room temperature, *N*-allyl propiolamides **33** undergo rapid intramolecular cycloisomerization to give the corresponding aza-bicyclo[3.2.0]hept-6-en-2-ones **34** in good to high yields (Scheme 13a). The mechanism of this cyclization was proposed based on density functional theory (DFT) calculations, determining that the reaction proceeds *via* tandem formal [2 + 2] cycloaddition/skeletal rearrangement.[39] Curiously, when the reaction was carried out under air atmosphere in 2,2,2-trifluoroethanol, the tricarbonyl compounds **35** were obtained in yields ranging from 41 to 86% instead of the desired bicyclic γ-lactam products (Scheme 13b).[40]

In 2011, Qian and Zhang published an efficient protocol for the synthesis of 3-aza bicyclo[3.1.0]hexan-2-ones **37** *via* gold(I)-catalyzed intramolecular oxidation–cyclopropanation sequence of *N*-allyl propiolamides **36** (Scheme 14a). Thus, the optimized reactions revealed that the optimum condition for this reaction was the combination of [IPrAuCl] (5 mol%) and $AgNTf_2$ (5 mol%) as catalytic system, 4-acetyl-pyridine *N*-oxide (2.0 equiv.) as external oxidant, and MsOH (1.2 equiv.) as additive using DCM as the solvent, at 60 °C. Under optimized conditions, the reaction tolerated aryl substituted internal *N*-propargylamines **36** and gave final products **37** in moderate to high yields. However, the reaction fails for substrates bearing alkyl groups in the alkyne terminus. The author proposed mechanistic pathway for this reaction starts with the formation of π-complex **A** from the enyne **36** and gold species, followed by its oxidation by 4-acetyl-pyridine *N*-oxide to give α-oxo gold carbenoid **B**. Finally, an intramolecular cyclopropanation of intermediate **B** leads to the observed γ-lactams **37** (Scheme 14b).[41]

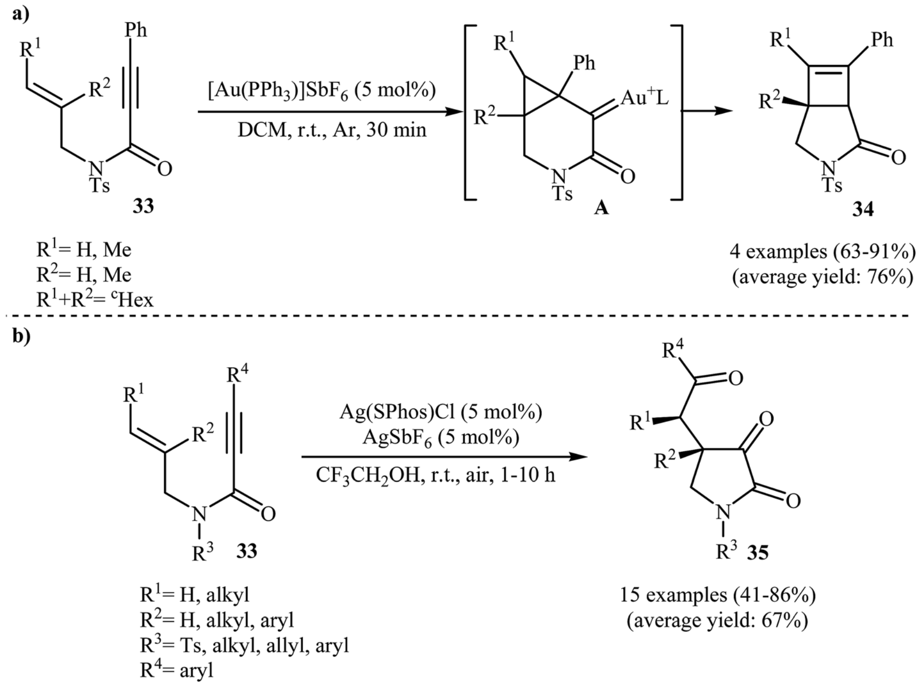
In a closely related study, Yeom and Shin also found that terminal *N*-allyl propiolamides **38** were converted to the corresponding cyclopropane-fused γ-lactams **39** *via* Au(I)-catalyzed oxidative cyclopropanation using [Au(SPhos)]Cl/$AgNTf_2$ combination as catalytic system and diphenyl sulfoxide as an oxidant in 1,2-dichloroethane at 60 °C (Scheme 15).[42]



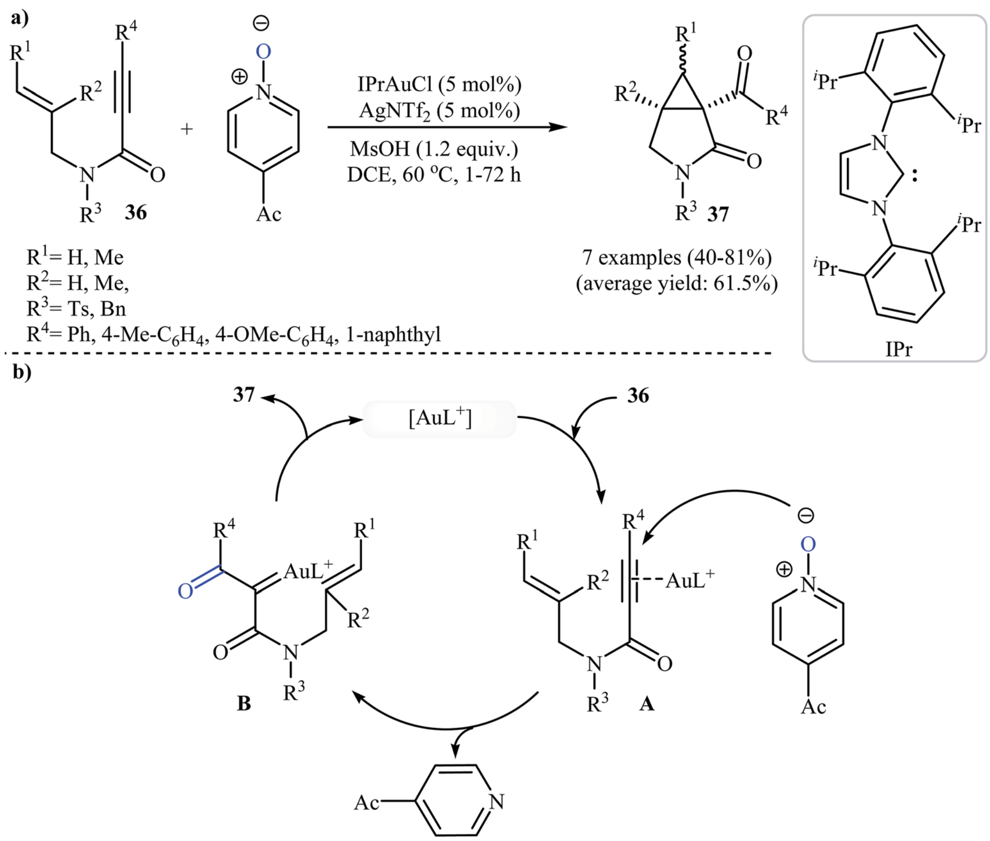
Scheme 11 Enantioselective Rh-catalyzed synthesis of α-chloromethylene-γ-butyrolactams **30** from *N*-allyl propiolamides **29**.

2.4 Silver

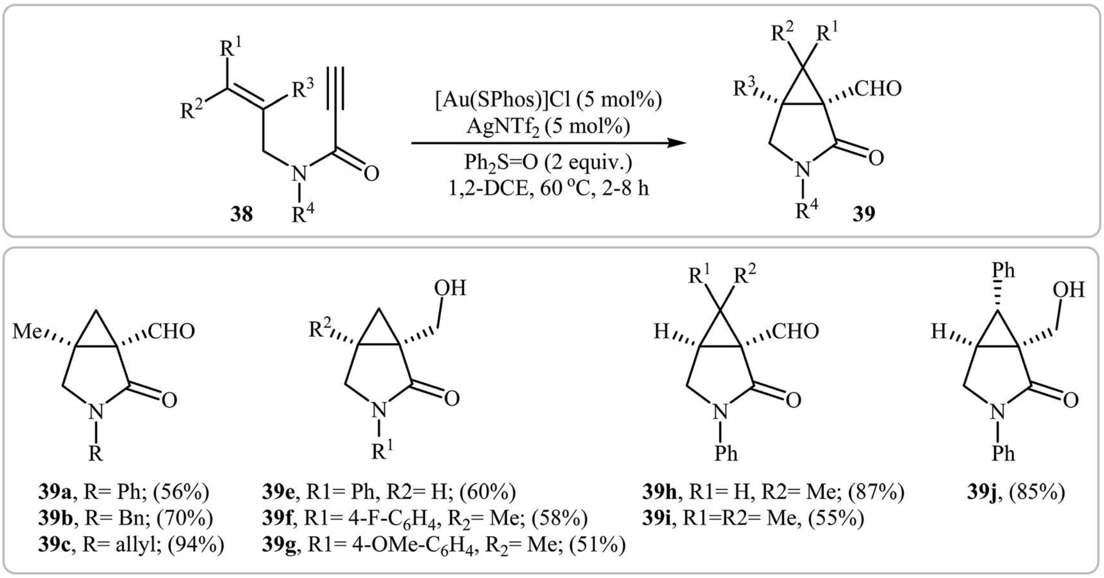
In 2013, Shin and co-workers have established a novel method for the preparation of Alder-ene-type 1,4-dienes. Thus in 1,2-dichloroethane, a $AgNTf_2$-catalyzed cycloisomerization of *N*-allyl propiolamides **40** furnished 5-*exo*-dig 1,4-diene products **41** in good to excellent yields (Scheme 16). Other silver catalysts such as $AgSbF_6$, AgOTf, and $AgBF_4$ were also found to promote the reaction, however, in lower yields. The authors claimed that the presence of C(5) carbonyl group in combination with Ag salts is essential for the selective formation of 5-*exo*-dig products.[43] Interestingly, when the reaction was carried out in the



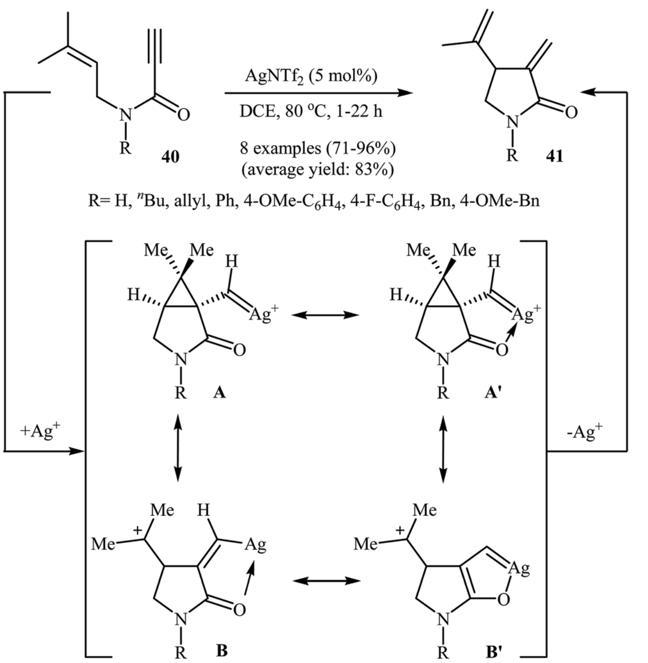
Scheme 13 (a) Au(I)-catalyzed cycloisomerization reaction of *N*-allyl propiolamides **33** to corresponding aza-bicyclo[3.2.0]hept-6-en-2-ones **34**; (b) Synthesis of tricarbonyl compounds **35** through Au-catalyzed cyclization of *N*-allyl propiolamides **33** under air atmosphere.



Scheme 14 (a) Synthesis of 3-aza-bicyclo[3.1.0]hexan-2-ones **37** *via* Au-catalyzed oxidative cyclopropanations of *N*-allyl propiolamides **36** with pyridine *N*-oxide; (b) mechanistic proposal for the reaction in (a).



Scheme 15 Synthesis of cyclopropane-fused γ-lactams **39** *via* Au(I)-catalyzed oxidative cyclopropanations of *N*-allyl propiolamides **38** with diphenyl sulfoxide.



Scheme 16 Ag(I)-catalyzed cycloisomerization of *N*-allyl propiolamides **40**.

presence of an Au(I) catalyst, the 6-*endo*-dig mode is preferred over 5-*exo*-dig.[44]

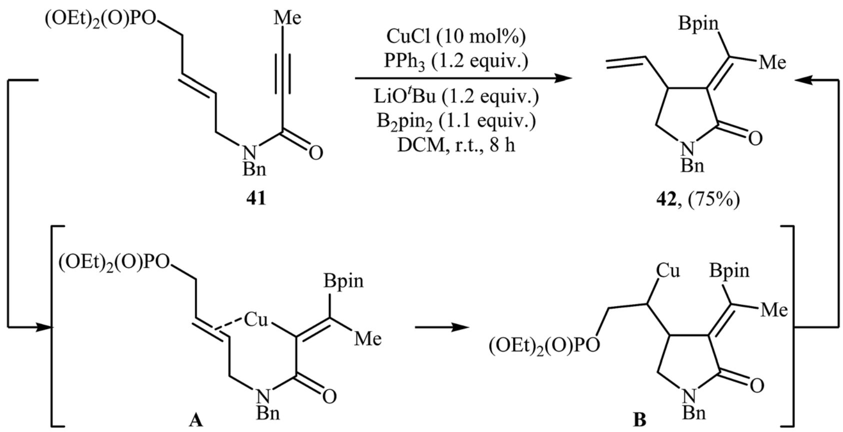
2.5 Copper

Copper-catalyzed cyclization of *N*-allyl propiolamides into γ-lactams has been scarcely studied; in fact, only one example of such a reaction was reported in the literature. In 2017, Bai and Zhu along with their co-workers have demonstrated the formation of α-alkylidene-γ-lactam **42** by room temperature $CuCl/PPh_3$-catalyzed borylative cyclization of 1,6-enynyl phosphate **41** with B_2Pin_2 as the borylation reagent (Scheme 17). Among the various solvents like THF, DMF, 1,4-dioxane, toluene, DCM, DCE, MeCN; DCM was the most efficient for this borylative cyclization. As shown in Scheme 1, the reaction starts with the formation of an alkenylcopper intermediate **A** *via* addition of the *in situ* generated borylcopper species (CuBpin) to the C–C triple bond of **41**, followed by addition of the alkenyl C–Cu bond to the intramolecular C–C double bond to generate alkylcopper species **B**. Finally, a β-elimination step leads to the final product.[45]

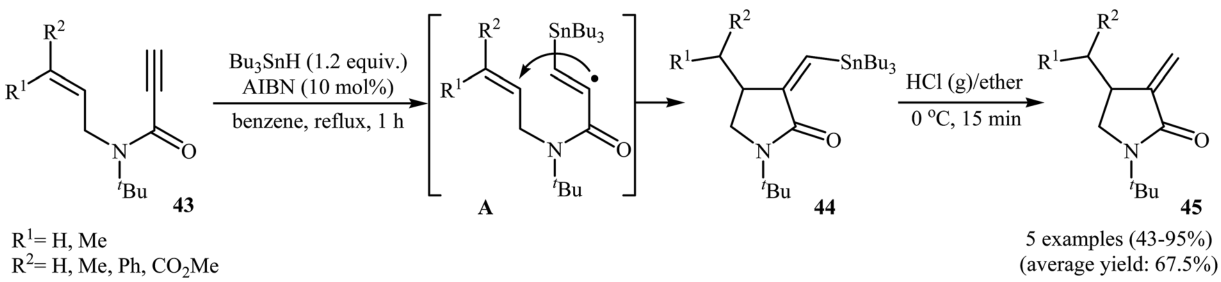
3. Radical mediated cyclizations

Synthesis of γ-lactams through radical mediated cyclization of propiolamide derivatives have been rarely studied. The earliest report on this chemistry have been published by Lee and Kang in 1993. They showed that treatment of *N*-allyl propiolamides **43** with 1.2 equiv. of Bu_3SnH and 10 mol% of AIBN in refluxing benzene gave α-stannylmethylene γ-lactams **44** *via* 5-*exo* cyclization of (α-aminocarbonyl-β-atannyl)viny radicals **A** that formed by the addition of stannyl radicals to the propiolamides triple bonds. The following destannylation reactions using HCl/ether system afforded moderate to excellent yields of corresponding α-methylene γ-lactams **45** (Scheme 18).[46] One main difference between this procedure and metal catalyzed reactions is that this protocol gives the products that having one C–C double bond in their structures while the latter affords the lactam derivatives that having two C–C double bond in their structures (compare Schemes 16 and 18).

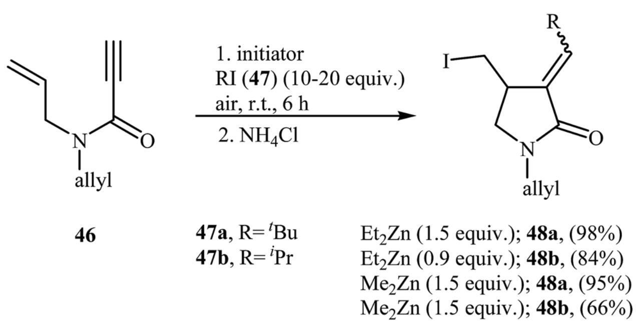
Fifteen years later, Feray and Bertrand reported the use of dialkylzinc mediated atom-transfer radical addition cyclization of *N*,*N*-diallylpropiolamides **46** into α-alkylidene-γ-lactams **48**.



Scheme 17 Cu(I)-catalyzed cyclization of 1,6-enynyl phosphate **41** reported by Bai and Zhu.



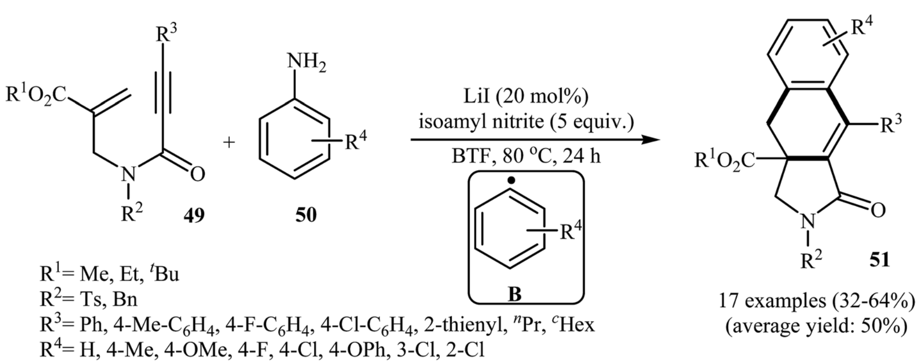
Scheme 18 Radical mediated synthesis of α-methylene γ-lactams **45** from *N*-allyl propiolamides **43**.



Scheme 19 Bertrand's synthesis of α-alkylidene-γ-lactams **48**.

Good to excellent isolated yields of γ-lactams **48** were obtained when propiolamides **46** was treated with either diethyl or dimethylzinc in the presence of alkyl iodides **47** and oxygen at room temperature (Scheme 19).[47]

More recently, an interesting cascade radical cyclization of *N*-allyl propiolamides **49** toward the synthesis of polycyclic γ-lactams **51** was reported by Studer *et al.* Thus, the reaction of *N*-allyl propiolamides **49** with aryl radicals **B**, generated *in situ* from commercially available anilines **50**, in benzotrifluoride afforded biologically important γ-lactams **51** in moderate yields (Scheme 20). The cyclization shows good functional group tolerance, including methoxy, chloro, flouro, and ester



Scheme 20 Construction of polycyclic γ-lactams **51** *via* cascade radical cyclization of *N*-allyl propiolamides **49**.

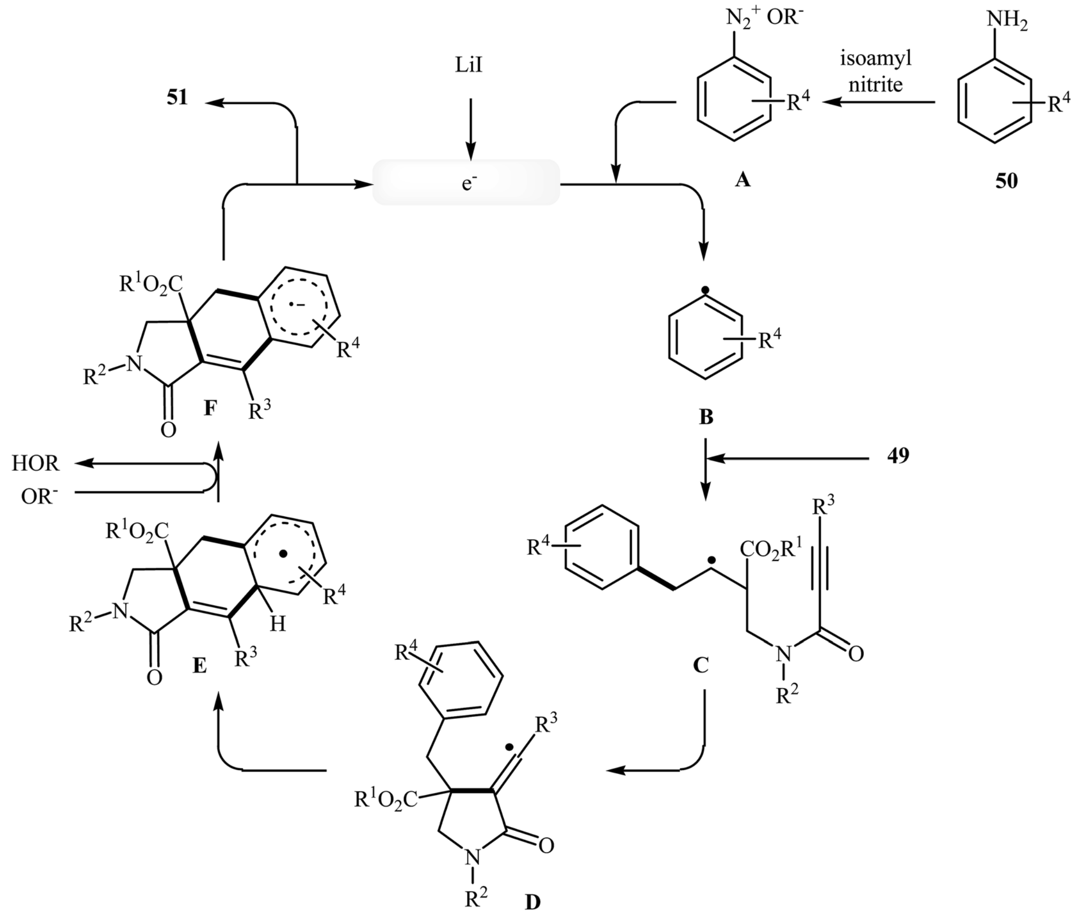


Fig. 2 Mechanistic proposal for the formation of **51**.

functionalities. It is noted that the strategy could be efficiently extended to the synthesis of polycyclic pyrrole and γ-butyrolactone derivatives. The mechanism shown in Fig. 2 is proposed for this transformation. It consists of the following key steps: (i) initial formation of diazonium salt **A** *via* reaction of aniline **50** with isoamyl nitrite; (ii) interaction of **A** with LiI to afford the aryl radical **B**; (iii) chemoselective radical addition of **B** to the activated alkene of *N*-allyl propiolamides **49** to give tertiary alkyl radical **C**; (iv) 5-*exo* cyclization of radical **C** leading to vinyl radical **D**; (v) intramolecular cyclization of radical **D** onto the arene produces the cyclohexadienyl radical **E**; (vi) deprotonation of **E** with alcoholate derived from isoamyl nitrite to afford arene radical anion **F**; and (vii) oxidation by liberating an electron gives polycyclic γ-lactam product **51**.[48]

4. Conclusion

γ-Lactams are at the heart of a number of natural products and synthetic pharmaceuticals that display an impressive variety of biological properties including antibacterial, antimicrobial, anticonvulsant, antidepressant, anti-inflammatory, antitumor, antimalarial, and antidiabetic properties. Several commercially available drugs, including brivaracetam, piracetam, levetiracetam, oxiracetam, seletracetam, aniracetam, ans phenylpiracetam are derived from γ-lactam-core entities. This biological activity has made the synthesis of γ-lactams quite attractive, and a large number of straightforward and robust methods for the construction of these cores established. In modern organic synthesis, intramolecular cyclization reactions are particularly important tools allowing the generation of at least one cycle in a single step with high atom economy, cost efficiency, and operational simplicity. As illustrated, the intramolecular cyclization of easily available *N*-allyl propiolamides into γ-lactam derivatives has gained a great deal of interest in recent years as useful alternative procedures. High atom and step economy, simplicity of operation, and good yields are the salient features of these reactions. Hopefully, this procedure will be employed in the synthesis of biologically important and complex natural γ-lactam-based compounds in future studies.

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