Role of Transition Metal Reagents in β-Lactam Synthesis: New Paradigms

Shamsher S. Bari, Aman Bhalla and Jitender Bhalla

Abstract 2-Azetidinones or β-lactams constitutes a well acknowledged class of antibiotics for about 80 years. The synthetic and biological aspects have attracted considerable interest of the research community around the world. Their applications as key synthons for biologically active natural/unnatural compounds, valuable building blocks and diverse pharmacological activities have accelerated the efforts in β-lactam synthesis. In this regard, transition metal reagents have provided enormous opportunities for revealing novel and selective approaches for the preparation of these heterocycles. Present chapter reviews the recent developments (2005–2015) made in β-lactams synthesis using various transition metal reagents. The introductory paragraph highlights the significance of the β-lactams chemistry followed by an overview of general synthetic methodologies of β-lactam synthesis. The other sections of this article deal with the various synthetic methodologies using transition metal reagents.

Keywords Transition metal reagents · 2-Azetidinones · β-Lactams Diastereoselectivity · Enantioselectivity

Abbreviations

Å	Angstrom
Ac	Acetyl
Ar	Aryl
Bu	Butyl
^{i}Bu	*Iso*-Butyl
^{t}Bu	*Tert*-Butyl
Bn/Bz	Benzyl
[bmIm]	1-Butyl-3-methylimidazolium
°C	Degree centigrade

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CAC	Chloroacetyl chloride
Cbz	Carboxybenzyl
$CHCl_3$	Chloroform
CO	Carbon monoxide
Cy_2NH	Dicyclohexylamine
Dba	Dibenzylideneacetone
D	Deuterium
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
De	Distereomeric excess
Ee	Enantiomeric excess
Et	Ethyl
ERGs	Electron releasing groups
EWGs	Electron withdrawing groups
G	Gram
H	Hour
LDA	Lithium diisopropylamide
MeOH	Methyl alcohol
MWI	Microwave irradiation
Mg	Microgram
Min	Minute
mL	Millilitre
mmol	Millimole
Me	Methyl
Ms	Mesylate
NCS	*N*-Chlorosuccinimide
Nu	Nucleophile
Ph	Phenyl
Piv	Pivaloyl
Pr	Propyl
^{i}Pr	*Iso*-Propyl
PMB	*P*-Methoxybenzyl
PMP	*P*-Methoxyphenyl
Ppm	Parts per million
SDS	Sodium dodecyl sulphate
TBS	*Tert*-Butyldimethylsilyl ether
TBDPS	*Tert*-Butyldiphenylsilyl ether
ThP	Thiophene

TMSCl	Trimethylsilyl chloride
TMSQD	Trimethylsilylquinidine
Tr	Trityl
Ts	Tosyl
p-TSA	*P*-Toluenesulfonic acid
THF	Tetrahydrofuran

1 Introduction

Heterocyclic compounds have occupied a very crucial place in the field of pharmaceutical industry. Both small as well as large heterocycles have proved their importance as biologically active compounds. The discovery of β-Lactam heterocycles as antibiotics has undoubtedly remained a milestone in the history of chemotherapy [1–5]. This has contributed extensively towards the improvement of human health throughout the 20th century. After their successful use as antibacterial agents in clinics, the synthetic and biological aspects have been highly exploited in the past few decades [6, 7]. As a result, many reports are available in the literature describing newer methodologies for the preparation of β-lactam ring [8], their diverse activity profile [9–12] and their synthetic application in organic chemistry [13–20].

The potential of β-lactam antibiotics has occupied a central role in the vigil against bacterial infections over the past few decades. Staudinger [21] was the pioneer who synthesized β-lactam heterocyclic ring for the first time. However, the actual credit for the emergence of research activity worldwide in this class of heterocycles goes to Fleming's landmark discovery of penicillin in 1929 [22]. The chemistry of β-lactams has always been in the forefront in synthetic organic chemistry since the discovery of penicillin [22] and cephalosporin [23] which are still being used as successful antibiotics. Other widely used antibiotics are aztreonam, nocardicins, thienamycin (Fig. 1) all of which contain azetidin-2-one heterocycle as a core structural feature. Recent addition to this category is trinems which are tricyclic carbapenems which act as broad spectrum β-lactamase inhibitors [24].

Large numbers of β-lactam antibiotics are known so far which are obtained either naturally or synthesized chemically. These β-lactam antibiotics can be broadly categorised under various classes (Fig. 2). In all the classes, β-lactam antibiotics have bicyclic structure in which β-lactam ring is either fused with saturate/unsaturated five/six membered carbocyclic ring except monobactams which are monocyclic β-lactams.

Unfortunately, the war with microorganisms is relentless and has led to significant bacterial resistance to the most commonly used members of this class of antibiotics [25]. The bacterial resistance to β-lactam antibiotics caused by their widespread use in the past decades has motivated a growing interest in the

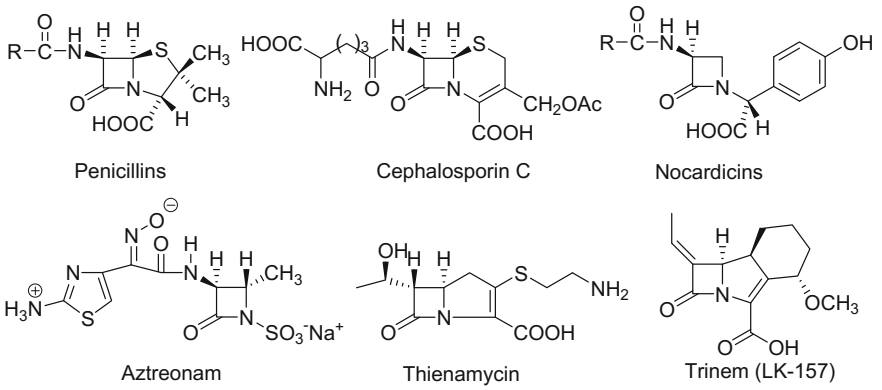


Fig. 1 β-Lactam antibiotics

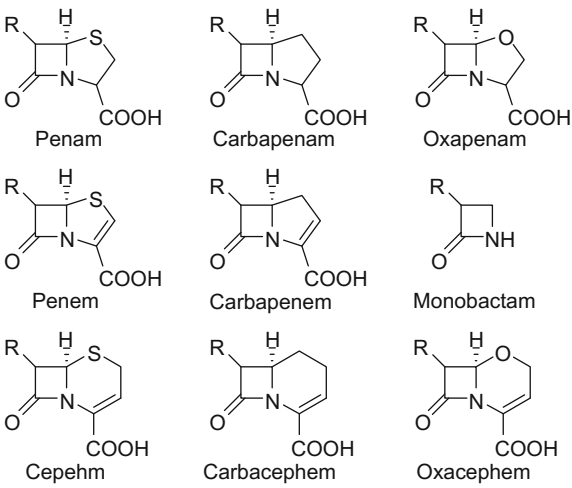


Fig. 2 Different classes of β-lactam antibiotics

preparation and biological evaluation of new types of β-lactams, which will overcome the defence mechanisms of the bacteria. In turn researchers have responded with investigations into novel β-lactams, which are stable to β-lactamases and retain high potency and broad activity in vitro and in vivo [26, 27].

2 Synthesis of β-Lactams

The first successful total synthesis of penicillin-V was carried out by Sheehan and Henry Logan [28] in 1958 by the ring closure of natural penicilloic acid. The synthetic approach was improved by preparing 6-aminopenicillanic acid (6-APA)

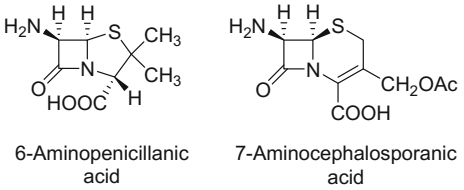


Fig. 3 Precursors of penicillins and cephalosporins

and acylating this directly to penicillin. Today, a number of synthetic mono- and bicyclic compounds such as monobactams, penams, cephams, carbapenems etc. have been developed due to the easy technical accessibility of penicillins and cephalosporins parent compounds namely 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA) (Fig. 3).

In earlier days, more focus was paid on the synthesis of β-lactam antibiotics from 6-APA and 6-ACA. The continuous efforts made in the β-lactam chemistry led to the discovery of various methodologies for the synthesis of β-lactam heterocycles. Significant advancement has been made towards developing novel strategies for the stereoselective synthesis of monocyclic β-lactams [1–5, 29–31]. The basic methodologies can be broadly divided into two categories [31] i.e. Cycloaddition and Cyclization.

2.1 Cycloaddition Reactions

Cycloaddition reaction is one of the most important and useful tool for the construction of β-lactam ring **I** with high efficiency and atom economy (Fig. 4). The most popular among these is Staudinger [2+2] cycloaddition reaction between ketene and imine [32]. Other common cycloaddition reactions aimed at β-lactams synthesis are enolate-imine condensation [33, 34] and isocyanates-vinyl ethers condensation [35, 36].

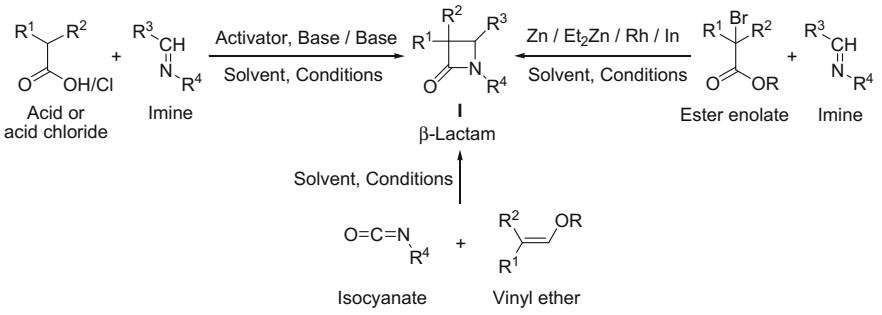


Fig. 4 Synthesis of β-lactams via cycloaddition reactions

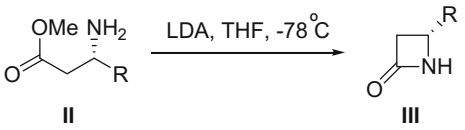


Fig. 5 β-Lactam synthesis via N1–C2 bond formation

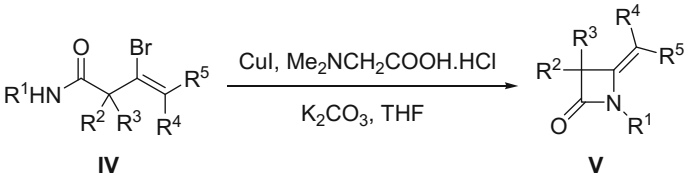
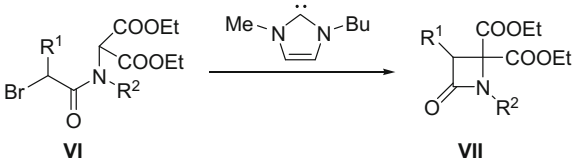


Fig. 6 β-Lactam synthesis via N1–C4 bond formation

Fig. 7 β-Lactam synthesis via C3–C4 bond formation



2.2 Cyclization Reactions

These reactions involve synthesis of β-lactam heterocycles via formation of N1–C2 bond (N-acylation), N1–C4 bond (N-alkylation) and C3–C4 bond (C-alkylation). These methods are not very common since they require appropriately substituted substrate. For example, N1–C2 bond formation occurs via N-acylation of β-amino acids/esters (Fig. 5) and N1–C4 bond formation (Fig. 6) can be achieved through N-alkylation of substrates having β-leaving groups (such as β-halo enamides, β-amino esters, β-hydroxamate esters and β-amino alcohols) [2–5, 31, 33]. Construction of β-lactam ring via formation of C3–C4 bond is a rare method (Fig. 7) [1–5, 33, 37]. However, intramolecular nucleophilic substitution reaction has been utilised for this purpose.

2.3 Miscellaneous

Apart from already discussed strategies for β-lactam synthesis, there are other methods which include ring expansion, carbonylation reaction and C–H insertion. These methods generally accompanied with the use of transition metal reagents.

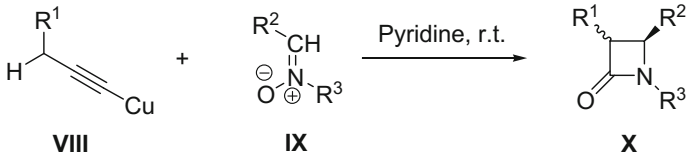


Fig. 8 β-Lactam synthesis via Kinugasa reaction

Fig. 9 β-Lactam synthesis via aziridine ring expansion

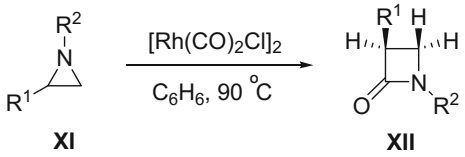
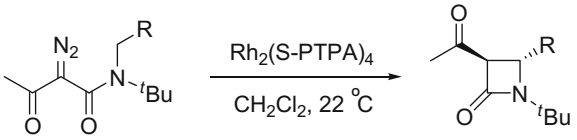


Fig. 10 β-Lactam synthesis via C–H insertion



A popular and direct method for the synthesis of β-lactam heterocycles which has gain much interest of the synthetic chemists in past few decades, is developed by Kinugasa and Hashimoto about 40 years ago (Fig. 8) [38]. It involves reaction of various nitrones with copper (I) acetylide in pyridine to afford β-lactams in good yields. Afterwards, many reports are available on this unique methodology for β-lactam synthesis [39, 40].

In addition to the classical methods, many other alternative strategies has been developed providing greater structural diversity in β-lactam synthesis. Some of these are transition metal catalysed ring expansion (Fig. 9) [41] and C–H insertion (Fig. 10) [42].

Last ten years have witnessed novel approaches for the synthesis of β-lactams using transition metal reagents. The transition metals used in β-lactam synthesis are mainly belonging to the later half of the d-block elements (Fig. 11). Hence, it is imperative to compile these studies in order to reveal new insights of β-lactam synthetic chemistry. This chapter focuses to update recent findings on synthesis of β-lactams using transition metal reagents during past ten years (2005–2015).

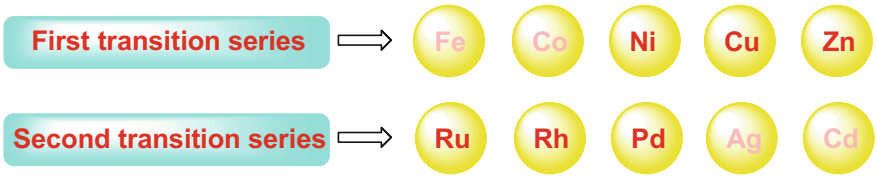


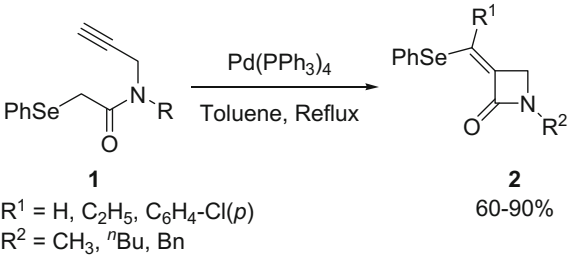
Fig. 11 Transition metals used for β-lactams synthesis

3 β-Lactam Synthesis Using Transition Metal Reagents

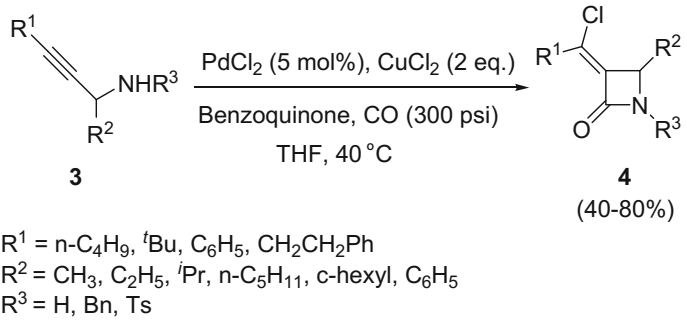
Kambe and co-workers [43] have described the formation of α-alkylidene-β-lactams **2** in good yields via intramolecular selenocarbamoylation of alkynes **1** using palladium catalyst (Scheme 1). The reaction was found to be highly selective and favours the formation *Z* product with *Z*/*E* ration of up to 100. Synthesis of conjugated lactams and thio/seleno incorporated cyclobutanones can also be achieved by using this catalytic system. They have also proposed the mechanism involving the role of palladium-alkyne coordination.

Ma et al. [44] have carried out the cyclocarbonylation of propargylic amines **3** in the presence of $CuCl_2$ and benzoquinone catalysed by palladium chloride to afford (*E*)-α-chloroalkylidene-β-lactams **4** (Scheme 2) in moderate to good yields. The formation of five membered product or (*Z*)-isomer was not observed at all. Furthermore, the reaction of optically active propargylic amines has resulted in the product formation in moderate yields with high *ee* (up to 98%).

Tang and co-workers have described an efficient methodology for the enantioselective synthesis of β-lactams utilising Cu(II) salts for the first time in Kinugasa reaction [45] (Scheme 3). It involves reaction of terminal alkynes **5** with nitrones **6** to afford β-lactams **7**–**8** in moderate to good yields. The reaction was catalysed by ^{i}Pr-trisoxazoline/$Cu(ClO_4)_2$ system resulting in high *ee* (up to 85%). The distereoselectivity was highly dependent upon terminal alkynes. Most of the alkynes afforded *cis*-β-lactams as compared to propiolates which prefers *trans* product. Moreover, secondary base were found to be better in producing higher enantioselectivities.



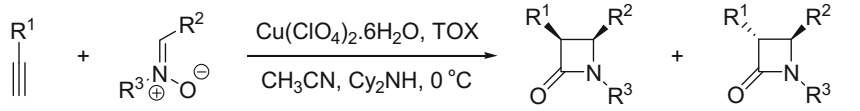
Scheme 1 Synthesis of 3-alkylidene-β-lactams via $Pd(PPh_3)_4$ catalysed intramolecular cyclisation



3 **4** (40-80%)

R^1 = n-C_4H_9, ^{t}Bu, C_6H_5, CH_2CH_2Ph
R^2 = CH_3, C_2H_5, ^{i}Pr, n-C_5H_{11}, c-hexyl, C_6H_5
R^3 = H, Bn, Ts

Scheme 2 $PdCl_2$ catalysed synthesis of α-alkylidene-β-lactams



5 **6** **7** *cis*-β-Lactam **8** *trans*-β-Lactam

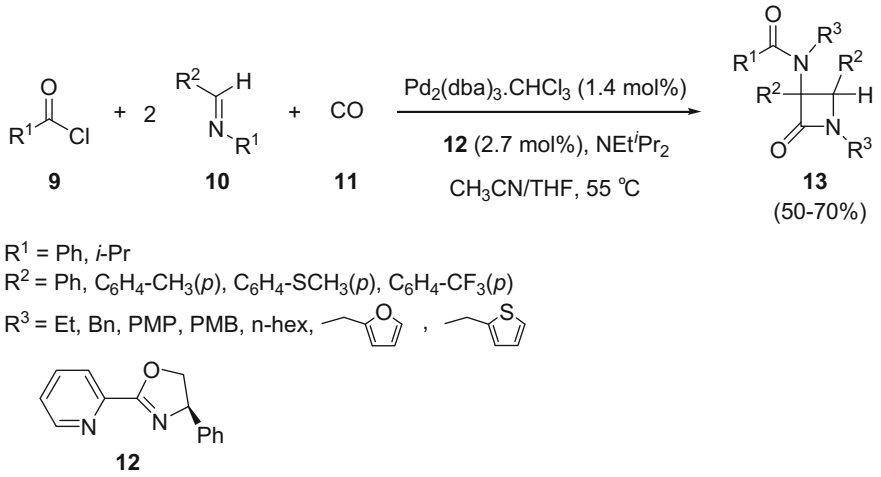
R^1 = Ph, C_6H_4-CF_3(*p*), $SiMe_3$, COOEt, 1-Cyclohexenyl
R^2 = Ph, C_6H_4-CF_3(*p*), C_6H_4-CH_3(*p*), C_6H_4-OCH_3(*p*), c-hex, α-furyl
R^3 = Ph, C_6H_4-Br(*p*), C_6H_4-CH_3(*p*), C_6H_4-OCH_3(*p*), Ph, C_6H_4-COOEt(*p*), CH_2Ph

Scheme 3 Enantioselective synthesis of 2-azetidionones via $CuClO_4$/TOX mediated Kinugasa reaction

A novel and direct synthesis of 3-amido-β-lactams **13** via palladium catalysed multicomponent approach (Scheme 4) using easily available substrates has been reported by Arndtsen et al. [46]. It involves one pot coupling of CO **11**, imines **10** and acid chlorides **9** and resulted in the formation of product in good yields. This methodology is also applicable where instead of two molecules of same imine, two different imines (i.e. different substitutions/groups) are used. However, in this case, the selectivity is reduced and mixture of β-lactams was obtained.

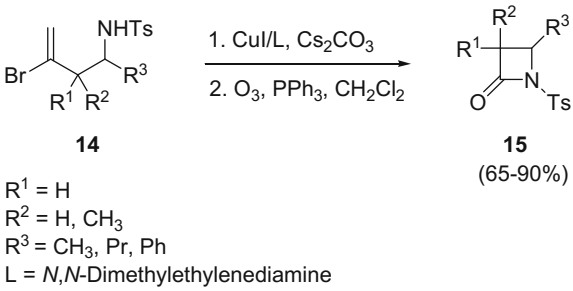
Li et al. [47] have reported an efficient route for the synthesis of 2-alkylidene azetidines and azetidinones **15** via intramolecular N-vinylation of N-tosyl-3-halo-3-butenylamines **14** catalysed by copper halide (Scheme 5). Appropriate amines underwent Ullmann type coupling in the presence of CuI and *N*,*N*′-dimethylethylenediamine to yield 2-alkylideneazetidines which subsequently oxidised to corresponding 2-azetidinones in good yields.

Troisi and co-workers [48] have reported palladium catalysed stereoselective synthesis of polyfunctionalized β-lactams **18**–**21** (Scheme 6). The allyl bromides **16** underwent [2+2] carbonylative cycloaddition with appropriate Schiff's base to afford β-lactams **18**–**19** having heteroaryl and alkenyl moiety at C-4 and C-3 β-lactam ring. Further functionalisation at C-3 and C-4 position was achieved through generation



Scheme 4 Palladium catalysed one pot multicomponent synthesis of β-lactams

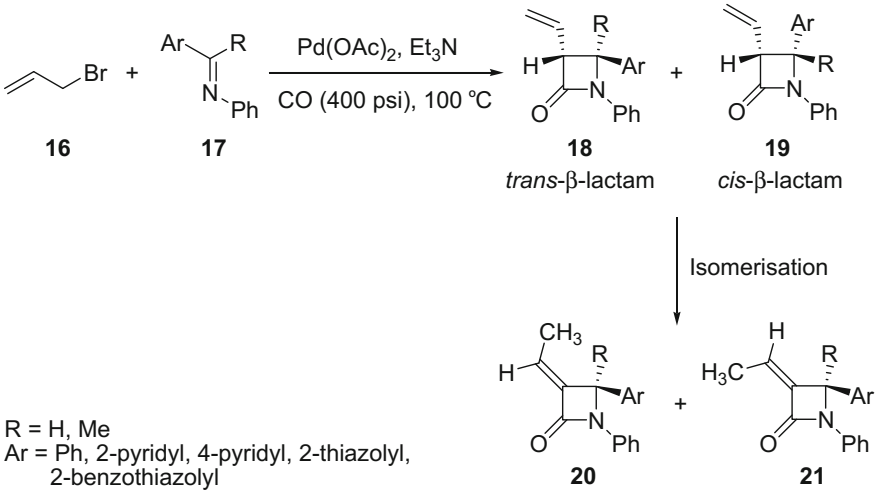
Scheme 5 Preparation of β-lactams via copper salt mediated intramolecular N-vinylation



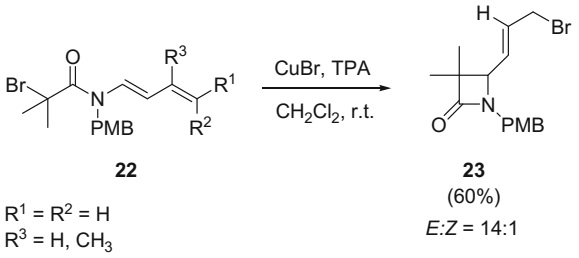
of stable anion followed by capturing by various electrophiles. In some cases, α,β-unsaturated carbonyl structures were obtained due to isomerisation.

Clark et al. [49] have described regiochemical aspects of cyclisation of halo-dienamides **22** using copper (I) catalyst to afford β-lactams **23** (Scheme 7). Substituted dienamides **22** in the presence of copper halide and tripyridyl amine undergo cyclisation to afford 5-*exo* or 6-*endo* product. Further, reaction of 3-substituted dienamides produces β-lactams via 4-*exo* cyclisation. The reaction is highly dependent upon type of diene causing termination of reaction via halogen atom transfer or radical-radical coupling or elimination or trapping with oxygen.

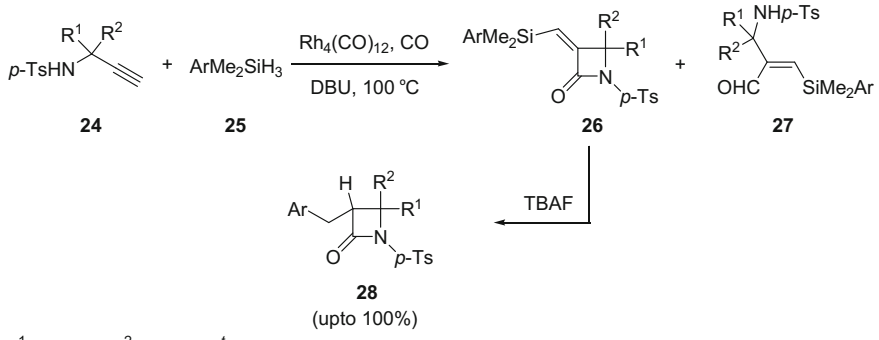
An efficient methodology for the synthesis of highly functionalised β-lactams **26** via rhodium complex catalysed silylcarbocyclisation of propargyl amides **24** (Scheme 8) has been reported by Salvadori et al. [50]. Tosyl amides **24** in the presence of catalytic amounts of DBU, reacts with hydrosilanes **25** to furnish α-silylmethylene-β-lactams **26** in good yields. In case of dialkyl functionalised



Scheme 6 Divergent synthesis of polyfunctionalised β-lactams using palladium acetate



Scheme 7 Regioselective syntheses of β-lactams using copper halide mediated cyclisations

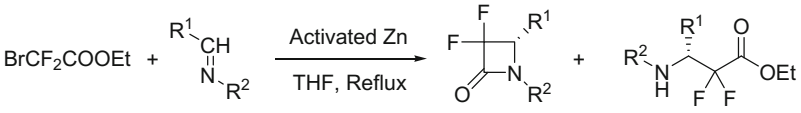


Scheme 8 Chemoselective synthesis of 2-azetidinones using tetrarhodium dodecacarbonyl

propargyl amides, the reaction has resulted in high chemoselectivity towards β-lactams regardless of hydrosilane. These β-lactams further undergo TBAF mediated desilylation with migration of aryl group with high distereoselctivity (up to 100%).

Jubault and co-workers [51] have discussed a highly stereoselective and chemoselective approach for the synthesis of gem-difluoro-β-lactams **31** making use of Reformatsky reaction (Scheme 9). It involves reaction of ethylbromodifluoroacetate **29** and imines **30** in the presence of activated zinc metal. The reaction was highly stereoselective towards β-lactams **31** (*R*)-phenylglycinol and (*R*)-methoxyphenylglycinol as R^1. Moreover, distereoselectivity can be easily reversed by modifying the amines.

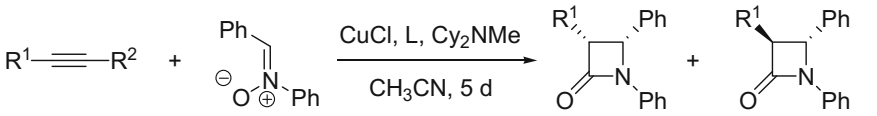
An efficient synthesis of chiral β-lactams **35–36** via HETPHOX/Cu (I) mediated asymmetric Kinugasa reaction (Scheme 10) has been reported by Guiry and co-workers [52]. The reaction of diversely substituted terminal alkynes **33** with nitrones **34** catalysed by HETPHOX ligands afforded β-lactams **35–36** in good yields with moderate *ee* (up to 53%). Diasteroselectivity is highly dependent on



29 **30** **31** **32**

R^1 = Ph, 3-pyridyl, 4-pyridyl
R^2 = *n*-pentyl, ^{t}Bu, Ph, PMB, 4-pyridyl, C_6H_4-NO_2(*p*), C_6H_4-CN(*p*), C_6H_4-CF_3(*p*), 4-F(*p*), C_6H_4-OMe(*o*), (*R*)-phenylglycinol, (*R*)-methocyphenylglycinol, α-(*R*)-methylbenzylamine

Scheme 9 Preparation of β-lactams via activated Zn mediated Reformatsky reaction



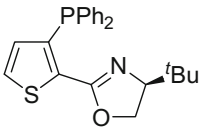
33 **34** **35** **36**

cis-β-lactam *trans*-β-lactam

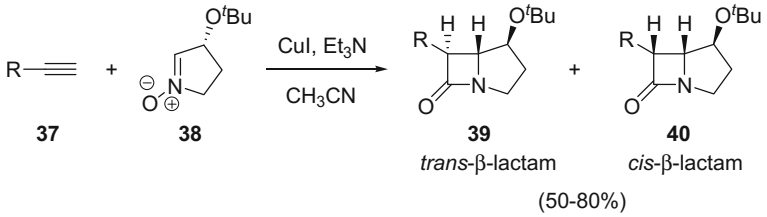
up to 80% conversion
ee up to 53%

R^1 = H, D
R^2 = Ph, C_6H_4-OCH_3(*p*), C_6H_4-CF_3(*p*), C_6H_3-$(CF_3)_2$(*m*,*m*)

L =

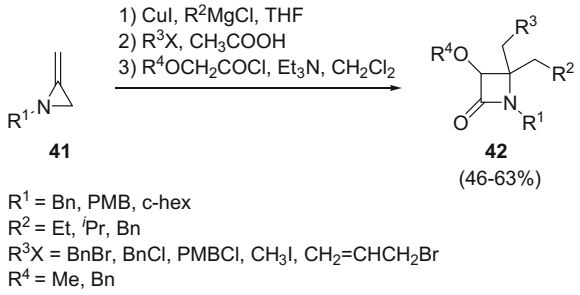


Scheme 10 Cu(I)/HETPHOX mediated asymmetric synthesis of β-lactams



Scheme 11 Diastereoselective synthesis of carbapenam analogues via Kinugasa reaction

Scheme 12 Synthesis of 2-azetidinones via CuI mediated ring opening reaction of aziridines

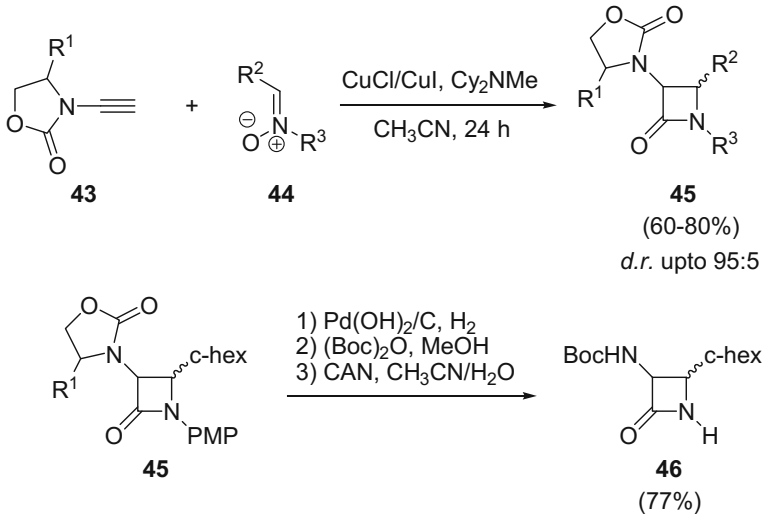


substitution on alkynes. *trans*- selectivity (1:9, *ee* 53%) was observed with 3,5-trifluoromethyl phenylacetylene while reversal of selectivity was observed (>9:1) with phenylacetylene.

Chemielewski and co-workers [53] have carried out distereoselective synthesis of carbapenam analogues **39**–**40** via Kinugasa reaction between malic and tartaric acid derived non racemic cyclic nitrones **38** and terminal copper acetylide **37** (Scheme 11). The diastereoselectivity of the reaction was mainly controlled by 3-*tert*-BuO group and resulted in the formation of 5,6-*cis*-carbapenam **40** as major product. Further, addition of hydrazine has enhanced the reaction yield in some cases by minimizing the side reactions.

Shipman et al. [54] have discussed a rapid approach for the synthesis of 1,3,4,4-tetrasubstituted-β-lactams **42** in good yields via one pot multicomponent reaction (Scheme 12). The conversion of 2-methylene aziridine **41** to β-lactams **42** involves sequential formation of three carbon-carbon bonds i.e. aziridine ring opening, C-alkylation and Staudinger cycloaddition. The aziridine ring opening reaction was catalysed by copper iodide. However, diastereoselectivity was very low.

Hsung and co-workers [55] have reported highly stereoselective approach for the preparation of chiral α-amino-β-lactams **46**. An important substrate i.e. N-protected-β-lactams **45** were synthesized via Kinugasa reaction between terminal alkynes **43** and ynamides **44** (Scheme 13). The products were obtained in good yields with high diastereoselectivities. The β-lactams **45** were transformed into



R^1 = Ph, ^{i}Pr, Bn, $CHPh_2$
R^2 = C_6H_5, C_6H_4-Br(*p*), styryl, 2-furyl, 1-naphthyl, 2-thiophenyl, c-hex
R^3 = C_6H_5, C_6H_4-Cl(*p*), C_6H_4-COOEt(*p*)

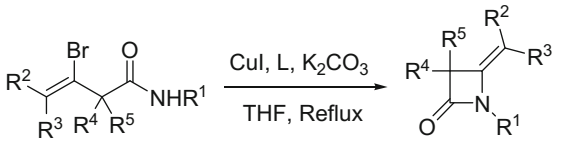
Scheme 13 Copper halide mediated stereoselective synthesis of 3-amino-2-azetidinones

chiral 3-amino-β-lactams **46** by palladium hydroxide mediated hydrogenation followed by protection-deprotection step.

Highly efficient and general approach for the synthesis of 4-alkylidene-β-lactams **48** via intramolecular C–N coupling vinyl bromides and amides (Scheme 14) has been described by Li et al. [56]. The cyclisation was preferably following 4-*exo* closure instead of 5-*exo*/6-*exo*/6-*endo* closure to yield β-lactams in excellent yields (up to 98%). This strategy was also applied for the preparation of medium sized lactams.

Konopelski et al. [57] have carried out direct synthesis of trityl protected β-lactams **51** (Scheme 15) for the first time. It involves formation of diazo β-ketoamide **50** derived from N-protected acetanilide **49** and N-tritylserine imidazolide, which upon decomposition furnished enantiomerically pure β-lactam derivatives. Moreover, expected product of the reaction i.e. 3-acyloxindole was also synthesized by the reaction between oxindole and Tr-Ser(OBn)-imidazole (an enantiomerically pure amino acid imidazolide).

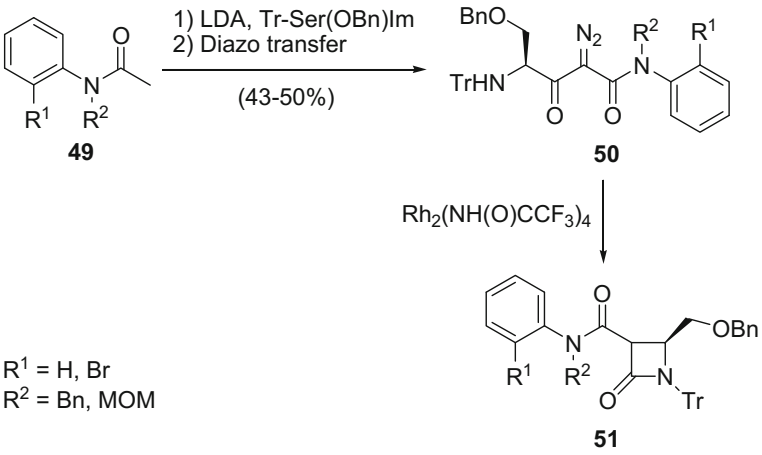
In an attempt towards polyfunctionalized N-alkyl-β-lactams **54**–**55**, Troisi et al. [58] have reported a highly efficient methodology involving palladium catalyzed carbonylative cycloaddition between allyl bromides **52** and heteroarylidene **53** (Scheme 16). The stereoselctivity is influenced by type of alkyl group at N of imines. Further, these β-lactams undergo functionalisation in stereoselective manner at C-3 and C-4 via generation of azetidinyl carbanion and capturing by electrophiles.



47 **48** (up to 99%)

R^1 = C_6H_5, C_6H_4-Me(*p*), C_6H_4-OMe(*p*), C_6H_4-COOMe(*p*), Bn, $C_{12}H_{25}$
R^2 = H, CH_3, C_6H_{13}
R^3 = H, CH_3, C_6H_{13}
R^4 = H, CH_3, Bn
R^5 = H, CH_3
L = $Me_2NCH_2COOH.HCl$

Scheme 14 Preparation of 4-alkylidene-2-azetidinones copper (I) catalysed intramolecular coupling



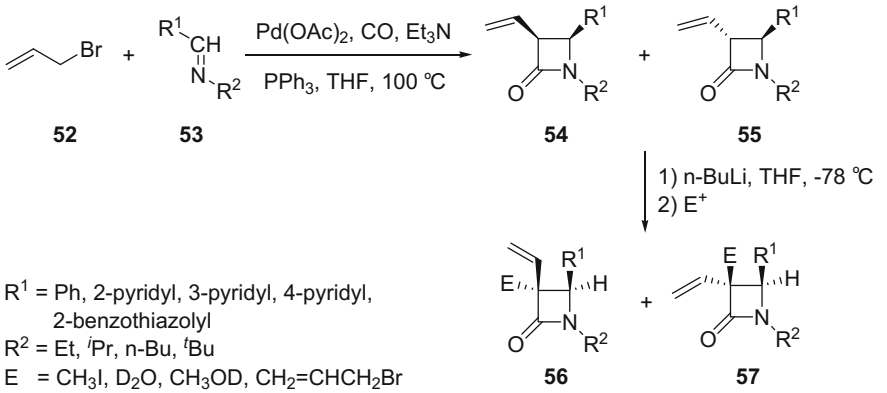
49 **50** **51**

R^1 = H, Br
R^2 = Bn, MOM

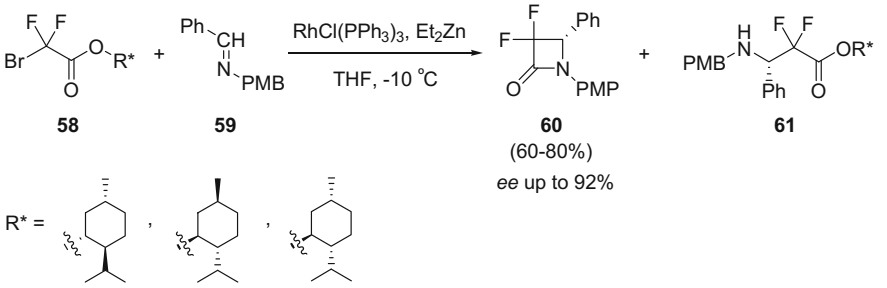
Scheme 15 Synthesis of enantiopure β-lactams

Ando and co-workers [59] have reported rhodium catalysed Reformatsky reaction (Scheme 17) for the synthesis of asymmetric difluoro-β-lactams **60** using (−)-menthyl as chiral auxiliary. The reaction was carried out between imine **59** and menthylbromodifluoro acetate **58** in the presence of $RhCl(PPh_3)_3$ to afford (*S*)-difluoro-β-lactams **60** in moderate to good yields with high diastereoselectivity.

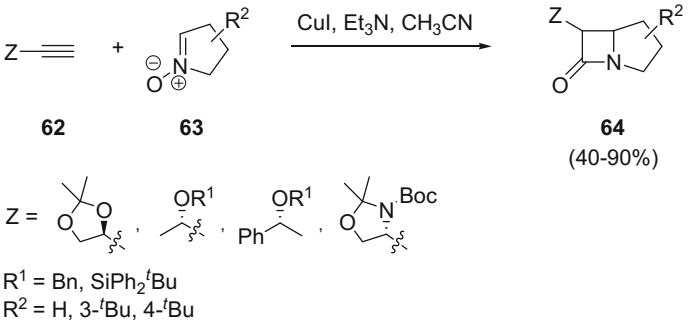
Chemielewski et al. [60] have performed asymmetric Kinugasa reaction of chiral acetylenes **62** and cyclic nitrones **63** to afford bicyclic β-lactams **64** or analogues of carbapenams in moderate to good yield (Scheme 18). The reaction was highly diastereoselective and mostly affords single diastereomer.



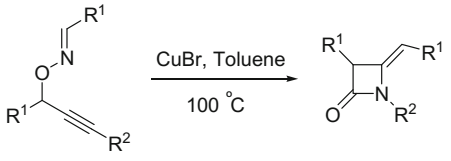
Scheme 16 Stereoselective synthesis of N-alkylated β-lactams and their functionalisation



Scheme 17 Rhodium catalysed asymmetric synthesis of β-lactams via Reformatsky type reaction



Scheme 18 Synthesis of bicyclic β-lactams via asymmetric Kinugasa reaction



65 **66**

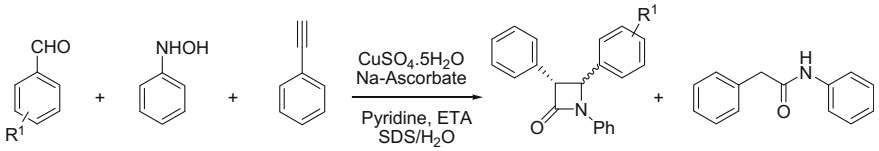
(60-90%)

E>*Z*

R^1 = n-Pr, c-hex, C_6H_5, C_6H_4-CF_3(*p*), C_6H_4-Cl(*p*), C_6H_4-OCH_3(*p*)

R^2 = C_6H_5, C_6H_4-CF_3(*p*)

Scheme 19 Preparation of 4-alkylidene-2-azetidinones via copper catalysed rearrangement of *o*-propargylarylaldoximes



67 **68** **69** **70** **71**

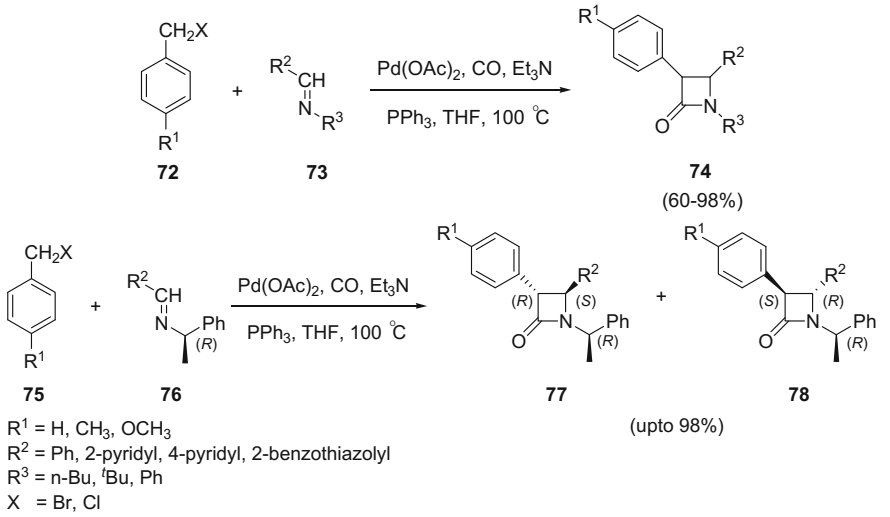
R^1 = H, 4-Me, 4-OMe, 3-OMe, 4-Br, 4-COOMe, 4-CN, 3-NO_2, 4-NO_2

Scheme 20 One pot synthesis of β-lactams via Kinugasa reaction in aqueous media

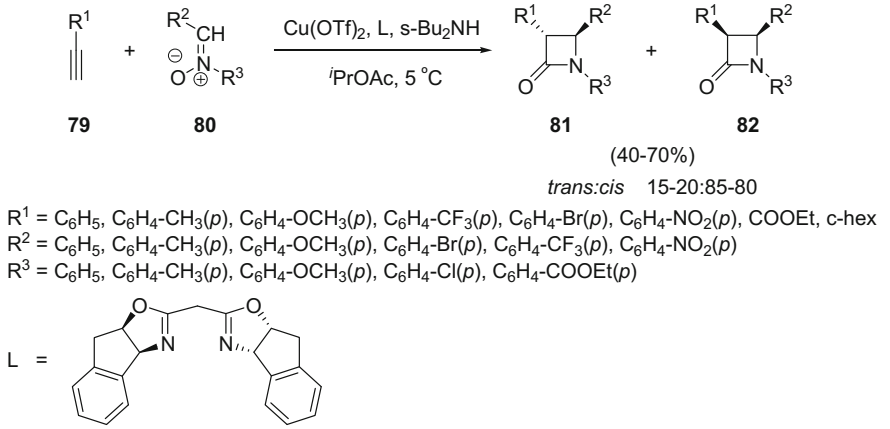
Copper catalysed rearrangement of appropriately substituted propargyl arylaldoximes **65** to furnish β-lactams **66** (Scheme 19) has been described by Nakamura et al. [61]. This skeletal rearrangement involves five bond cleavage in order to obtain the product. The products were obtained in moderate good yields. Further, aldoximes **65** having identical groups on oxime resulted in exclusive formation of β-lactam products. In case of alkyl substituents, *E*-isomer was obtained as major product with small amount of *Z* isomer.

Pezacki and co-workers [62] has reported micelle promoted multicomponent Kinugasa reaction catalysed by copper sulfate in aqueous media to afford monocyclic β-lactams **70** (Scheme 20). The reaction involves copper catalyzed coupling reaction between alkynes **69** and nitrones which are generated in situ. Various substituents play important role as they enhance the rate of reaction and also minimize the side reactions. Substitution of electron withdrawing groups on α-aryl group of nitrone produced better yields.

Novel series of 3,4-diaryl-2-azetidinones **74** has been prepared stereoselectively via palladium catalysed carbonylative [2+2] cycloaddition of heteroarylidene amines with benzyl halides **72** [63] (Scheme 21). Substrate scope of the reaction was also checked with chiral imines **76**, in which case separable mixture of chiral β-lactams **77–78** were obtained in good yields with high *trans* selectivity.



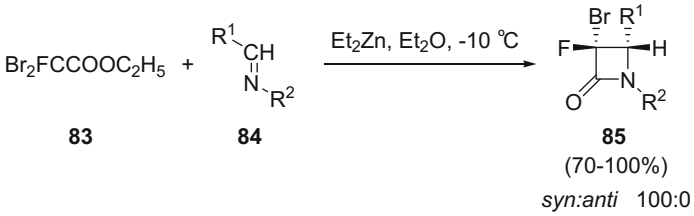
Scheme 21 Palladium catalysed carbonylative cycloaddition: Synthesis of 3,4-diaryl-β-lactams



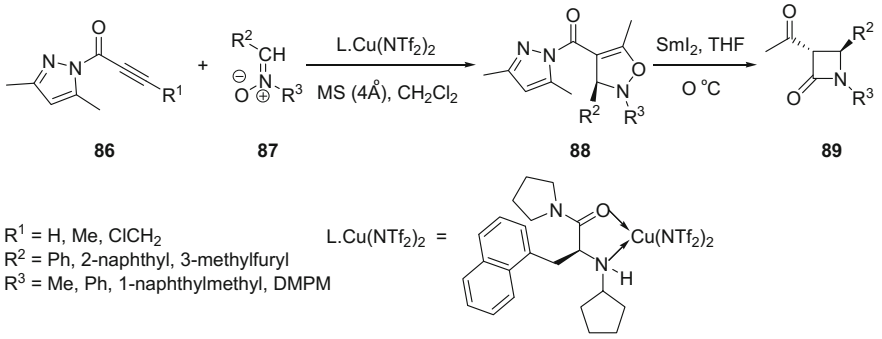
Scheme 22 IndaBox-Cu catalysed enantioselective synthesis of β-lactams

Otani et al. have carried out IndaBox-Cu mediated enantioselective synthesis of 2-azetidinones **81**–**82** via Kinugasa reaction [64] (Scheme 22). The reaction was performed between diversely substituted terminal alkynes **79** and nitrones **80** in the presence of a C_2-symmetric IndaBox ligand and $Cu(OTf)_2$. The reaction resulted in the formation of product favouring *cis* diastereomer and high enantioselectivities.

Tarui et al. [65] have reported diastereoselective and chemoselective synthesis of syn-α-bromo-α-fluoro-β-lactams **85** via Reformatsky reaction using diethylzinc



Scheme 23 Diethylzinc mediated synthesis of α-halo-β-lactams



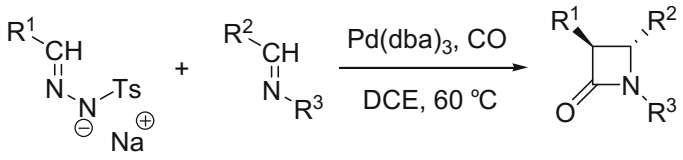
Scheme 24 Nickel catalysed diastereoselective functionalisation of α-halo-β-lactams

(Scheme 23). It involves the reaction of imines **84** and dibromofluoroacetate **83** to afford diastereomerically pure product in good yields. However, reaction using zinc metal produces poor chemoselectivity with the formation aziridine also.

Sakakura et al. [66] has reported 1,3-dipolar cycloaddition of propiolyl pyrazole and acrylo pyrazoles with nitrones **87** catalysed by chiral catalyst to yield **88** which can be transformed diastereoselectively into β-lactam derivatives **89** using samarium halide via N–O reductive cleavage (Scheme 24). The stereoselectivity towards anti product was achieved up to 99%.

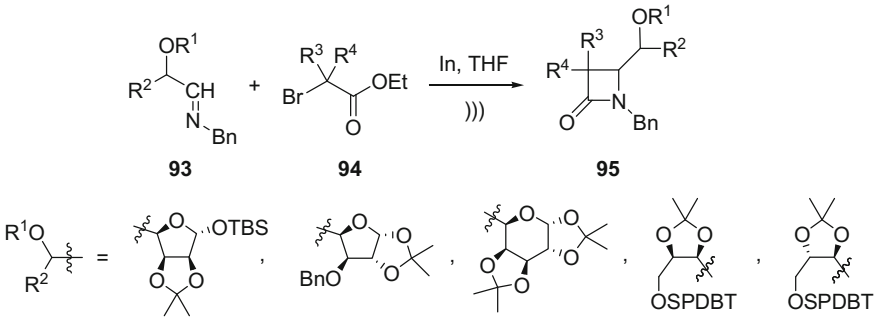
Li et al. [67] have carried out carbonylation of α,β-unsaturated tosyl hydrazones **90** in the presence of palladium catalyst to afford 2-azetidinones **92** with excellent yields (Scheme 25). The α,β-unsaturated tosyl hydrazones **90** undergo carbonylation followed by Staudinger [2+2] cycloaddition to yield the target product **92**. The reaction was highly selective towards *trans* isomer. Moreover, DFT studies suggests that palladium play a role in isomerisation of zwitterionic intermediate due to which *trans* product is formed predominantly.

Soengas and co-workers [68] have reported diastereoselective synthesis of sugar derived β-lactams **95** using indium metal under sonication (Scheme 26). This methodology is very simple and efficient involving reaction between various



R^1 = C_6H_5, C_6H_4-CH_3(*p*), C_6H_4-Cl(*p*), C_6H_4-COOMe(*p*), 2-naphthyl, 2-furyl
R^2 = C_6H_5, C_6H_4-OCH_3(*p*), C_6H_4-NO_2(*p*)
R^3 = CH_3, Bn, PMP

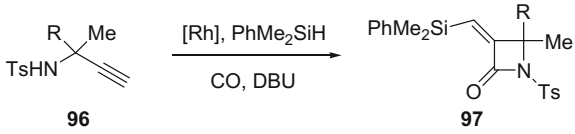
Scheme 25 Synthesis of β-lactams via palladium catalysed carbonylation-cycloaddition



R^3 = Me, Pr, Ph
R^4 = H, Me

Scheme 26 Diastereoselective synthesis of carbohydrate derived β-lactams

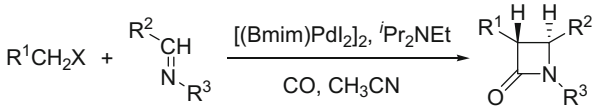
Scheme 27 Rhodium nanoparticles catalysed synthesis of 2-azetidinones



R = Me, Et, ^{t}Bu

substituted bromoesters **94** and carbohydrate imines **93**. 3-Mono and disubstituted 2-azetidinones were obtained in good yields.

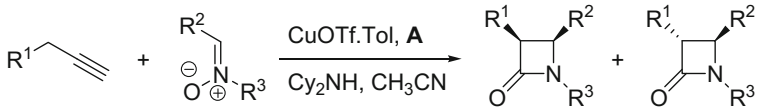
Aronica et al. [69] have synthesized functionalised β-lactams **97** starting from propargyl tosyl amides **96** via silylcarbocyclisation using rhodium nanoparticles as catalysts (Scheme 27). Rhodium nanoparticles were derived from mesitylene solvated Rh atoms and deposited on organic (PBI) or inorganic matrices (Al_2O_3 or Fe_2O_3). These nanoclusters were more active than similar commercially available reagents. The methodology is highly efficient and chemoselective.



98 **99** **100**

R^1 = C_6H_4-Cl(*p*), C_6H_4-Br(*p*), C_6H_4-Me(*p*), C_6H_4-OMe(*p*), C_6H_4-OMe(*o*), 1-naphthyl
R^2 = C_6H_5, C_6H_4-Cl(*p*), C_6H_4-Br(*p*), C_6H_4-Me(*p*), C_6H_4-OMe(*p*), C_6H_4-NMe_2(*p*), 1-naphthyl
R^3 = n-Pr, Bn, CH_2COOMe
X = Cl, Br, $OP(O)(OEt)_2$

Scheme 28 Preparation of *trans*-β-lactams via palladium/NHC catalysed carbonylation and cycloaddition



101 **102** **103** **104**

(60-98%)

d.r. 95:3 & *ee* 88-99%

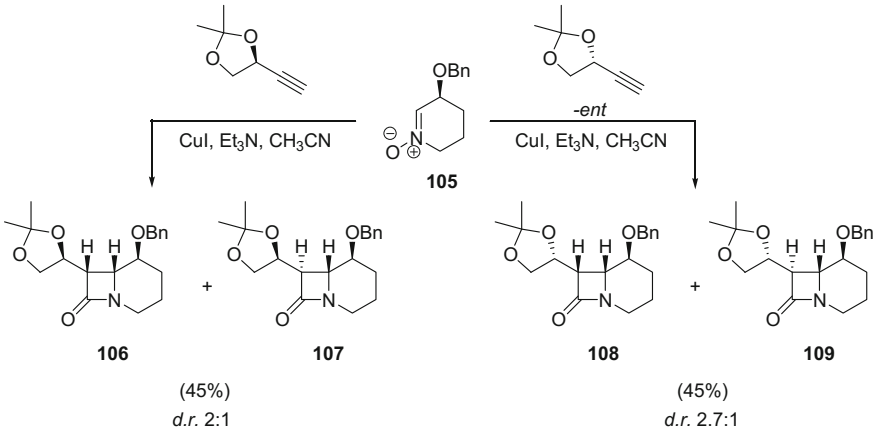
R^1 = Ph, C_6H_4-OMe(*p*), C_6H_4-Br(*p*), C_6H_4-Me(*p*), *n*-pentyl
R^2 = Ph, C_6H_4-OMe(*p*), C_6H_4-Br(*p*), C_6H_4-COOEt(*p*)
R^3 = Ph, C_6H_4-OMe(*p*), C_6H_4-Br(*p*), C_6H_4-Me(*p*), C_6H_4-Cl(*p*), C_6H_4-CF_3(*p*), C_6H_4-NO_2(*p*), 2-furyl

Scheme 29 Copper/tris(oxazoline) catalysed enantioselective synthesis of β-lactams

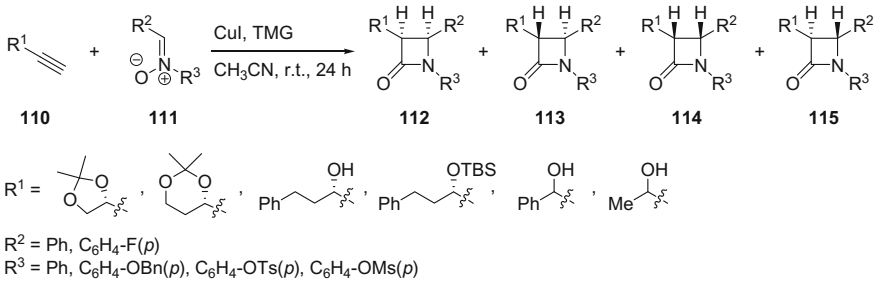
Huang et al. [70] have carried out synthesis of *trans*-β-lactams **100** stereoselectively via carbonylative cyclcoaddition reaction catalysed by palladium and N-heterocyclic carbene complex (Scheme 28). It involves reaction of various imines **99** with benzyl chlorides **98** or allyl derivatives in the presence of CO. This methodology provides high efficiency and excellent regioselectivities. Further, reaction under asymmetric environment affords moderate diastereoselectivities.

Chen and co-workers [71] have studied copper/tris(oxazoline) catalysed coupling reaction between alkynes **101** and nitrones **102** (Scheme 29). Use of chiral catalyst provides high diastereoselectivities and enantioselectivities, best among Kinugasa reaction reported so far. The enantiomeric purity of *cis* isomer can be achieved up to 99% via single crystallisation step.

Furman et al. [72] have reported asymmetric Kinugasa reaction between various acetylenes and six membered cyclic nitrones (Scheme 30). The reaction furnished the products **106**–**109** in low to moderate yields but high diastereoselectivity. The diastereoselectivity was also analysed by reaction of one chiral component with



Scheme 30 Asymmetric synthesis of bicyclic β-lactams



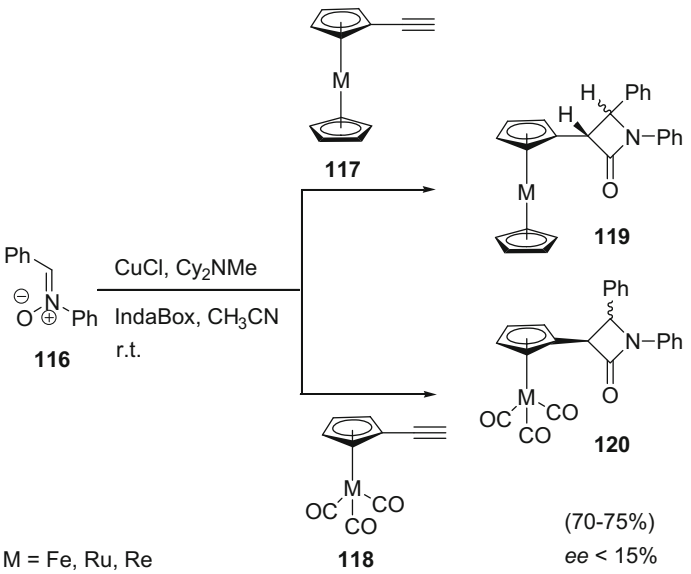
Scheme 31 Synthesis of 1,4-diaryl-2-azetidinones

another achiral entity or by taking both the substrates as chiral molecules. Similar reaction with dihydroisoquinoline derived nitrone furnished mixture of products.

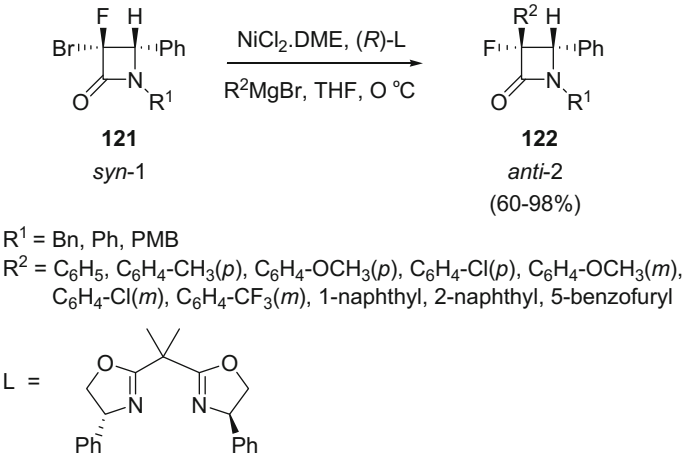
Asymmetric synthesis of 1,4-diaryl-β-lactams **112–115** has been synthesized with moderate diastereoselectivity via Kinugasa reaction by Chemielewski and co-workers [73] (Scheme 31). Nitrones bearing electron withdrawing groups (EWGs) provide best diastereoselectivities. The reaction is also feasible with unprotected chiral propargyl alcohols. These were subsequently oxidised/epimerised to furnish pure β-lactams.

In an effort towards the synthesis of metal substituted β-lactams derivatives **119–120**, Sierra et al. [74] have reported condensation reaction between diaryl nitrones **116** and alkynes substituted with sandwich and arene tethered carbene complexes **117–118** (Scheme 32). The method is applicable to sensitive metal fragments and has quite low diastereoselectivity and enantioselectivity.

A successful attempt towards α-arylation of α-bromo-α-fluoro-β-lactams **122** via $NiCl_2$ catalysed cross coupling reaction has been repoted by Tarui and co-workers

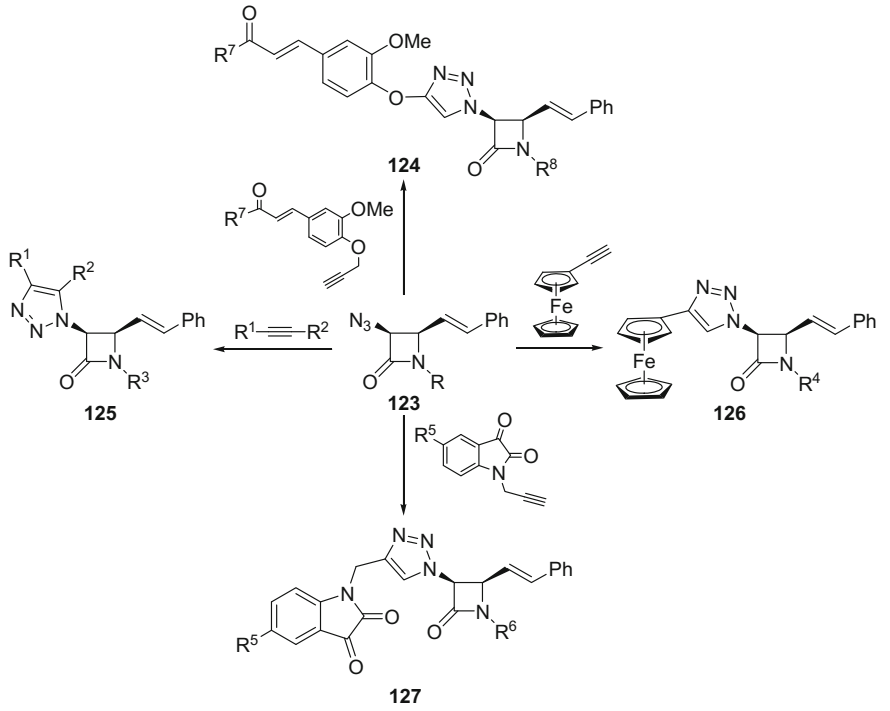


Scheme 32 Synthesis of metal substituted β-lactams



Scheme 33 Nickel catalysed α-arylation of α-halo-β-lactams

[75] (Scheme 33). The reaction was found to be general in case of variety of aryl Grignard reagents. The reaction was found to be highly diastereoselective resulting in the formation of *anti* diastereomer in excellent yields (up to 98%). This reaction is an excellent example of Kumada coupling reaction catalyzed by complex of Nickel and bis-(oxazoline).

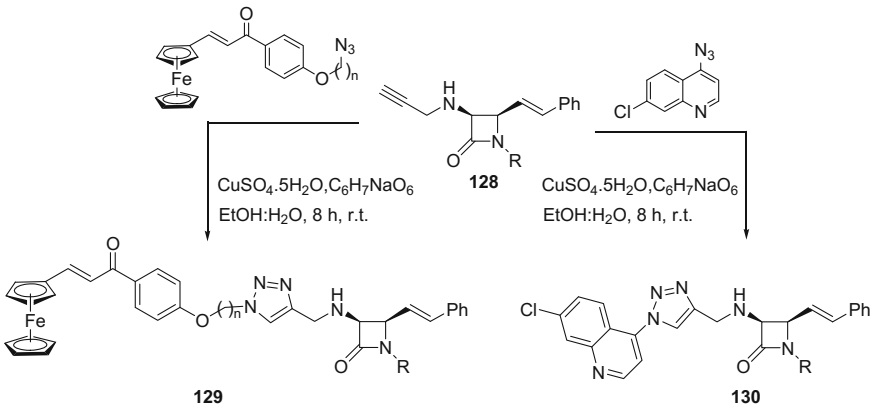


Reaction conditions: $CuSO_4.5H_2O$,$C_6H_7NaO_6$, EtOH:H_2O, 8 h, r.t.
R^1 = Ph, COOMe; R^2 = H, COOMe; R^3 = Ph, c-hex, C_6H_4-Cl(*p*), C_6H_4-Me(*p*);
R^4 = ^{n}Bu, ^{i}Bu, Ph, c-hex, c-hep, CH_2Ph, C_6H_4-Cl(*p*), C_6H_4-F(*p*), C_6H_4-CH_3(*p*), C_6H_4-CF_3(*p*);
R^5= H, F, Cl, Br, CH_3; R^6 = Ph, CH_2Ph, c-hex, C_6H_4-Cl(*p*), C_6H_4-F(*p*), C_6H_4-CH_3(*p*);
R^7 = C_6H_5, C_6H_4-OMe(*o*), C_6H_4-OCH_3(*p*), C_6H_3-$(OMe)_2$(o,*p*); R^8 = c-hex, C_6H_4-CH_3(*p*)

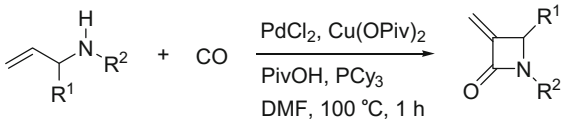
Scheme 34 Facile synthesis of β-lactam conjugates from 3-azido-β-lactam via copper catalyzed click reaction

The copper catalysed click reaction is successfully used by Kumar and co-workers [76–81] to synthesize novel 1,2,3-triazole tethered β-lactam conjugates **124–127**, **129–130** (Schemes 34 and 35). The starting substrate i.e. 3-azido-β-lactam **123** was condensed with various substituted alkynes via azide-alkyne click reaction to afford novel conjugate β-lactams **124–127** in excellent yields (Scheme 34). Similarly, 3-(prop-2′-ynylamino)-β-lactams **124** yielded hybrid β-lactams **129–130** (Scheme 35). All these novel heterocycles were screened for potential biological activities viz. antimalarial, antitubercular, antiparasitic and anticancer. Some of the compounds showed promising results.

Lei et al. [82] have synthesized α-methylene-β-lactams **133** via oxidative carbonylation of N-allylamines **131** using palladium catalyst (Scheme 36). The reaction was performed in the presence of carbon monoxide, an oxidant (copper acetate), an additive and a tertiary base. The methodology is simple, benign and



Scheme 35 Efficient synthesis of hybrid β-lactams from 3-propargylamino-β-lactam via copper catalyzed alkyne-azide condensation

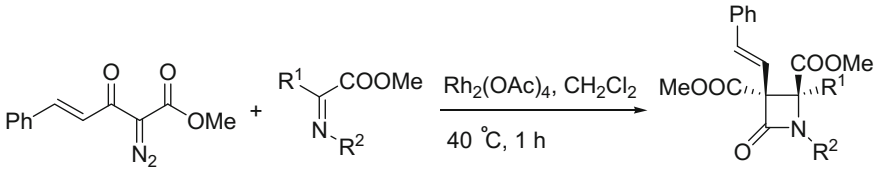


Scheme 36 Synthesis of β-lactams via palladium catalysed intramolecular oxidative carbonylation

highly selective to afford useful products. Further, DFT calculation has revealed the involvement of a four membered transition state.

Doyle and co-workers [83] have carried out the diastereoselective synthesis of β-lactams **136** via hetero Diels-Alders reaction between ketene derived from α-diazoesters **134** and α-carbonyl imine **135** in the presence of rhodium catalyst (Scheme 37). Similarly, the enonediazoacetate were reacted with aryldiazoacetate and anisyl azide in one pot multicomponent synthesis of β-lactams in quantitative yields.

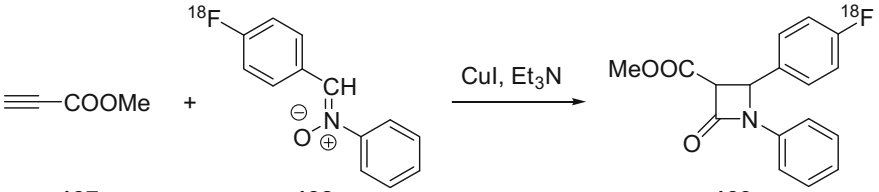
Neumaier and co-workers [84] have reported the synthesis of novel radiofluorinated β-lactams **139** via an efficient Kinugasa reaction (Scheme 38). It involves the treatment of a terminal alkyne **137** with fluorine labelled nitrone **138** in the presence of copper iodide and triethylamine to afford [^{18}F] labelled azetidin-2-ones **139** in very good yield. The reaction resulted in the formation of a mixture of *trans* and *cis*-β-lactams along with 4-[^{18}F]-fluorobenzylidene aniline as side product. The *trans*/*cis* ratio was significantly changed when different terminal alkynes were used.



134 **135** **136**

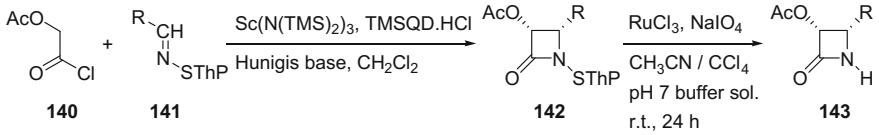
R^1 = Ph, Ac, C_6H_4-OMe(*p*), C_6H_4-NO_2(*p*)
R^2 = C_6H_4-OMe(*p*), C_6H_4-NO_2(*p*)

Scheme 37 Synthesis of β-lactams via rhodium catalysed Staudinger reaction



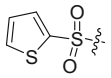
137 **138** **139**
(up to 75%)
trans:*cis* = 4:1

Scheme 38 Synthesis of radio [^{18}F] labelled azetidin-2-one derivatives via copper iodide mediated Kinugasa reaction



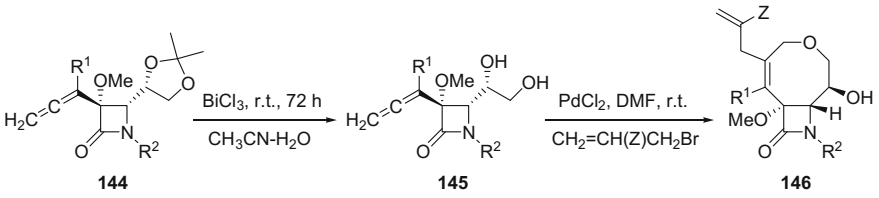
140 **141** **142** **143**

R = Ph, C_6H_4-Me(*p*), C_6H_4-Br(*p*), C_6H_4-F(*p*), C_6H_4-Cl(*p*), C_6H_4-CN(*p*), C_6H_4-Cl(*m*), C_6H_3-Cl_2(*m*,*m*)

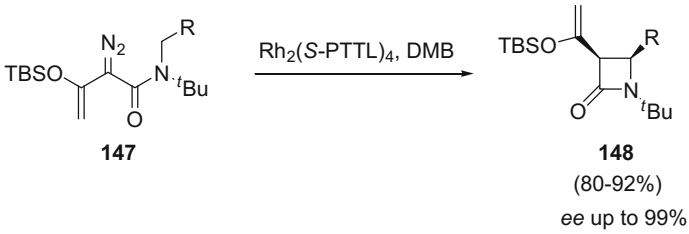
ThPS = 

Scheme 39 Asymmetric synthesis of N-unprotected β-lactams metal reagent mediated protection/deprotection

Calter and Wang [85] have discussed thiophene sulfonyl (SThP) as compatible protecting group for catalytic asymmetric synthesis of unprotected β-lactams **143** (Scheme 39). The N-protected β-lactams **142** were synthesized by the condensation reaction between acetoxyacetyl chloride **140** and thiophene sulfonyl imines **141** in the presence of a co-catalytic system of scandium (III) complex and silylated cinchona alkaloid.



Scheme 40 Palladium chloride catalyzed diastereoselctive synthesis of β-lactams fused with oxacycles

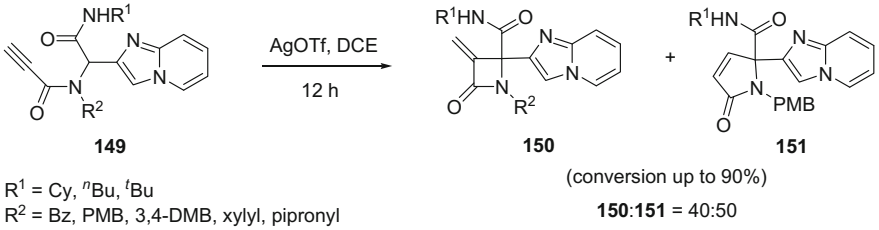


Scheme 41 Enantioselective synthesis of *cis*-β-lactams via rhodium catalyzed intramolecular C–H insertion

Alcaide and co-workers [86] have prepared various β-lactam adducts **146** in highly efficient, chemoselective and regioselective manner (Scheme 40). Initially, enantiopure β-lactam tethered allenic diols **145** were obtained from 4-dioxolane-β-lactams **144** by using bismuth trichloride. After this, β-lactam tethered allenic diols **145** undergo coupling reaction with allyl halides catalyzed by palladium chloride to afford bicyclic β-lactams **146** via 8-*endo* cyclisation selectively in good yields.

Xu et al. [87] have carried out enantioselective synthesis of β-lactam derivatives **148** from enoldiazoacetamides **147** via C–H functionalization (Scheme 41). The intramolecular C–H functionalization of enoldiazoacetamides **147** was achieved in excellent yields by using chiral dirhodium catalyst. The authors have also established the involvement of a cyclopropene intermediate complex by carrying out some model reactions. The reaction was highly selective and results in the formation of *cis*-β-lactams in high yields and high *ee*. The enantioselectivities were reduced when electron withdrawing groups were present on aromatic ring.

Li et al. [88] have reported a diversity-oriented regioselective approach for the preparation of β-lactams **150** and γ-lactams **151** via post-Ugi nucleophilic

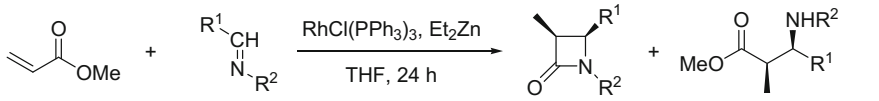


149 **150** **151**

R^1 = Cy, ^{n}Bu, ^{t}Bu
R^2 = Bz, PMB, 3,4-DMB, xylyl, pipronyl

(conversion up to 90%)
150:**151** = 40:50

Scheme 42 Synthesis of β-lactams and γ-lactams using silver catalyst



152 **153** **154** **155**

(up to 93%)
dr = 97:3

R^1 = C_6H_5, C_6H_4-CF_3(*p*), C_6H_4-COOMe(*p*), C_6H_4-OMe(*p*), C_6H_4-Cl(*p*), C_6H_4-Me(*p*), C_6H_4-Cl(*o*), C_6H_4-Cl(*m*), 1-naphthyl
R = Bn, Ph, PMP

Scheme 43 Synthesis of *syn*-β-lactams via rhodium catalyzed Mannich-type reduction

cyclisation (Scheme 42). The imidazopyridine anchored substrate **149** undergoes post-Ugi cyclisation by using silver catalyst to afford a mixture of β and γ-lactams **150**–**151** in good yields. Further, selectivity towards azetidin-2-ones was enhanced by using other metal catalysts. Moreover, substituted alkynes in place of terminal alkynes in the substrate led to the exclusive formation of γ-lactams.

Isoda et al. [89] have synthesized *syn*-β-lactams **154** diastereoselectively via rhodium catalyzed Mannich-type reduction (Scheme 43). The reaction between α,β-unsaturated esters **152** and diversely substituted imines **153** in presence of RhCl$(PPh_3)_3$ and diethyl zinc to afford *syn*-β-lactams in very good yields. The combination of rhodium and zinc reagent produces rhodium hydride complex which actually plays catalytic role. Further, various EWGs and ERGs did not cause any significant change in either yields or diastereomeric ratio.

4 Concluding Remarks

The research efforts towards synthesis of β-lactam heterocycles using transition metal reagents have attracted considerable interest in last 10 years. The Kinugasa reaction involving use of copper salts/reagents was of prime importance. The other methodologies involve carbonylation reaction using reagents of metals such as Pd,

Pt, Ni etc. The application of Rhodium nanoparticles in the synthesis of β-lactams presents vast scope in the future. Besides, most of the strategies resulted in excellent enantioselectivities (*ee*) and diastereoselectivities (*de*). The significant advancement will continue to encourage research in this field.

We would like to apologize to those scientists whose work may not have appeared in this review either due to the limited scope of the review or oversight.

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