KINUGASA REACTION: A FUTURE OF β-LACTAM ANTIBIOTICS

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Abstract: The β-lactam antibiotics are among the most commonly prescribed drugs in the world and their importance has been demonstrated by the isolation and syntheses of several classes of these agents. Of the synthetic routes used to access this interesting scaffold, the Kinugasa reaction utilizes a convergent strategy based on cycloaddition between readily available terminal alkynes and nitrones. Asymmetric versions involving chiral catalysts, chiral auxiliaries or chiral substrates have also been reported. Intramolecular Kinugasa reactions are also developed. β-turn based pharmacophore design became easy with the synthesis of peptidyl β-lactam by this reaction. This article gives a brief overview of the Kinugasa reaction and of recent advances since its discovery.

Keywords: β-Lactams, Synthetic methods, Intramolecular reaction, Asymmetric synthesis, Cycloaddition, Alkynes, Nitrones, Peptidomimetics.

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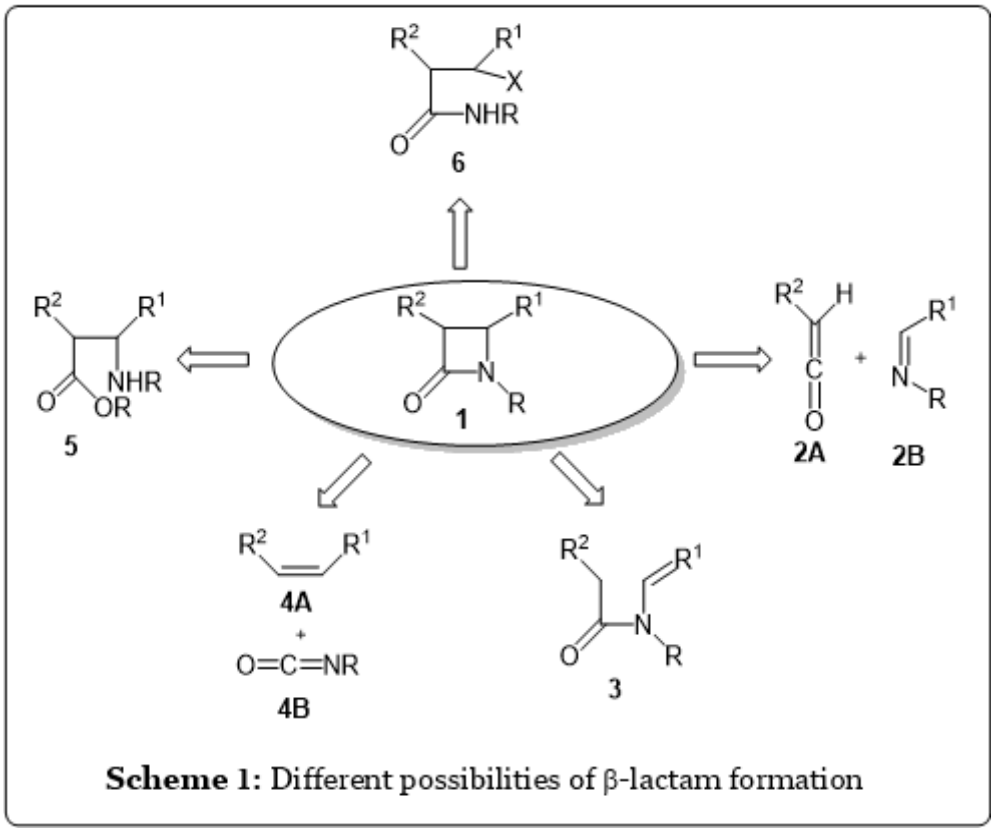
1. *Introduction*

Emergence of bacterial resistance is a growing problem.[1] Infectious diseases like septicemia were almost invariably fatal before the discovery of antibiotics. It is hard to imagine those dreadful days. When penicillin was first isolated at Oxford, [2] it quickly became the new wonder drug. Since then, other families of β-lactam antibiotics have been developed and their massive use worldwide continues to be the first line of defense against infectious pathogens. In later years, medicinal interest on these compounds expanded to other areas, such as mechanism based inhibitors of serine proteases[3] and as inhibitors of acyl-CoA cholesterol acyltransferase (ACAT).[4] Encouraged by these pharmacological applications, chemical synthesis of β-lactams has attracted much attention over the years. Chemists were challenged with the task of synthesizing the strained four member ring (2-azetidinone), which constitutes the nucleus of all β-lactam antibiotics. In spite of all the new developments, the antibacterial activity of β-lactams still remains at the centre stage of most of the research endeavors in β-lactam research.

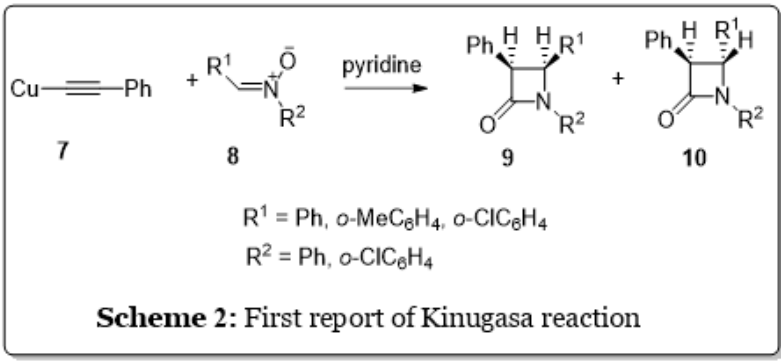
In pursuit of the goal towards the synthesis of β-lactams, a number of chemical methods have been developed, the approaches of which are described in **Scheme 1**. Some of the methods that involved [2+2] cycloaddition, are the ketene-imine cycloaddition, also known as the Staudinger reaction,[5] the metalloester enolate-imine cycloaddition,[6] the chromium carbene-imine reaction,[7] the isocyanate-olefin cycloaddition[8] and the nitrone-alkyne cycloaddition (actually a [3+2] cycloaddition) also known as the Kinugasa reaction.[9] In particular the latter method has provided a useful and economical entry to β-lactams, mainly due to the ready availability of both nitrones and alkynes but still this method is largely neglected in current practice of organic chemistry. In this article, recent developments of Kinugasa reaction for the synthesis of β-lactams including the asymmetric versions are reviewed.



Scheme 1: Different possibilities of β-lactam formation

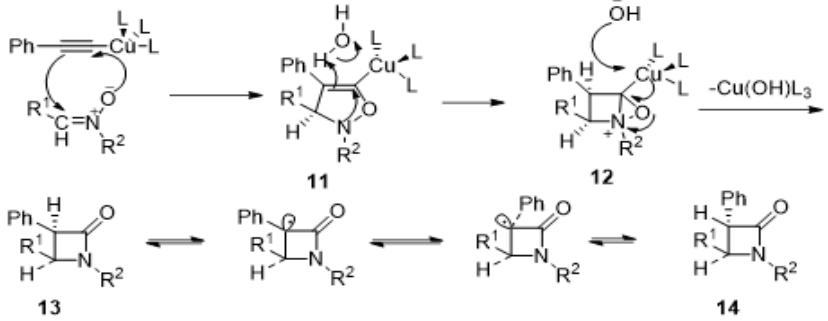
2. *Synthesis of β-lactams by Kinugasa Reaction*

The formation of β-lactams by the reaction of copper (I) acetylides and nitrones (**Scheme 2**) is known as Kinugasa reaction. The first report of this reaction, [10] published in 1972, depicted the formation of exclusively *cis*-products from phenyl acetylide (yields 51.2-60.2%) within 30 min to 1 h. The reaction was carried out using anhydrous pyridine both as solvent and base at room temperature under nitrogen atmosphere.



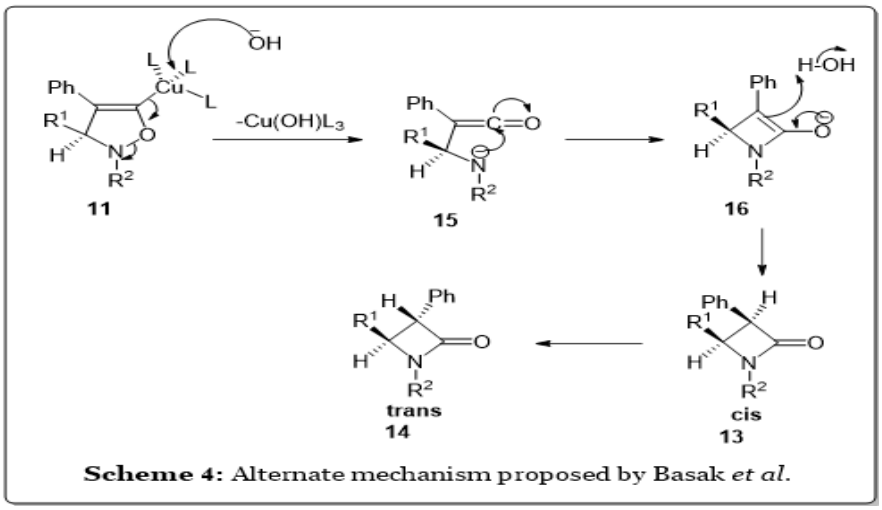
Scheme 2: First report of Kinugasa reaction

The formation of pyrrolinedinones or isoxazolines as side products was prevented in this reaction by the use of copper (I) phenyl acetylide as one of the reagent. The mechanism of this reaction as proposed by Ding and Irwin[11] is shown in **Scheme 3**.



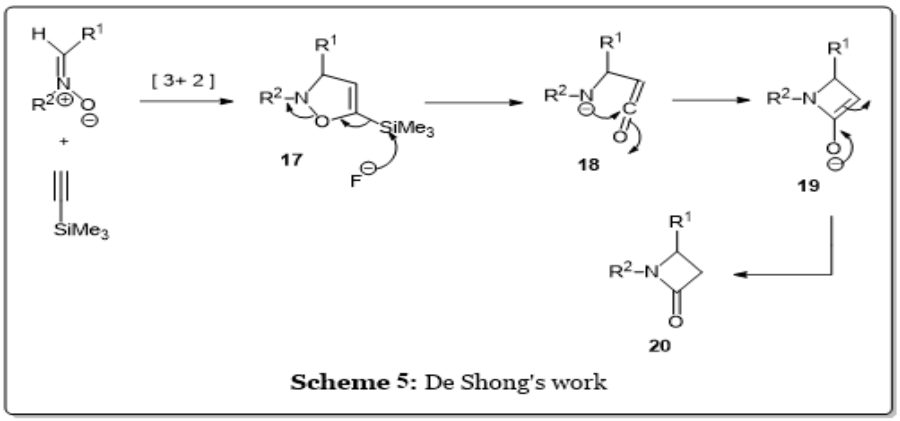
Scheme 3: Mechanism of Kinugasa reaction proposed by Ding and Irwin

One drawback of the proposed mechanism is the involvement of a highly strained fused bicyclic system comprising of a 3-membered oxaziridine and a 4-membered azetidine. An alternate mechanism can be put forward involving the formation of an intermediate ketene which is then followed by an intramolecular cyclization as shown in **Scheme 4**.



Scheme 4: Alternate mechanism proposed by Basak *et al.*

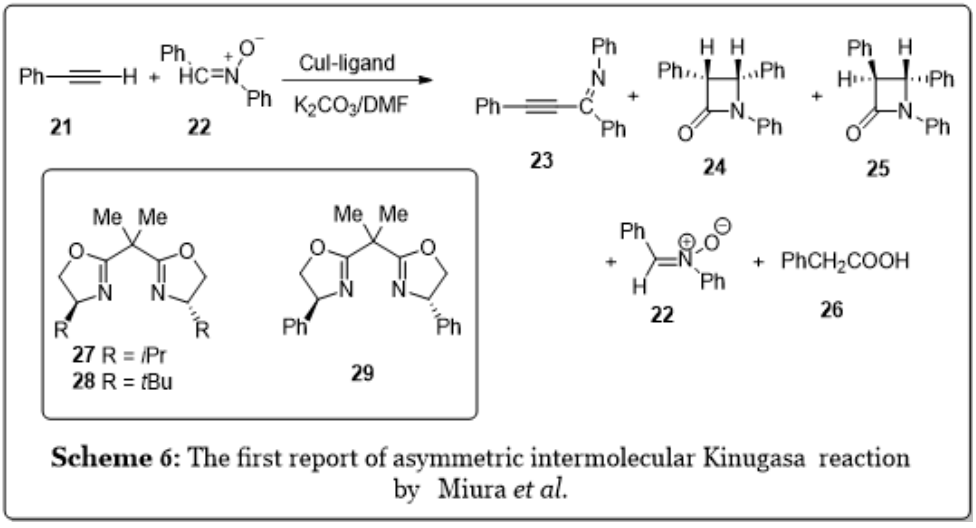
Although no definitive evidence exists to unambiguously prove either of the two mechanisms (like isolation or trapping of intermediates), the mechanism involving ketene intermediate appears to have gathered support by the work of De Shong[12] *et al.* The latter group has shown the formation of □-lactams *via* cycloaddition involving a nitrone and TMS-acetylene followed by desilylation with fluoride.



Scheme 5: De Shong's work

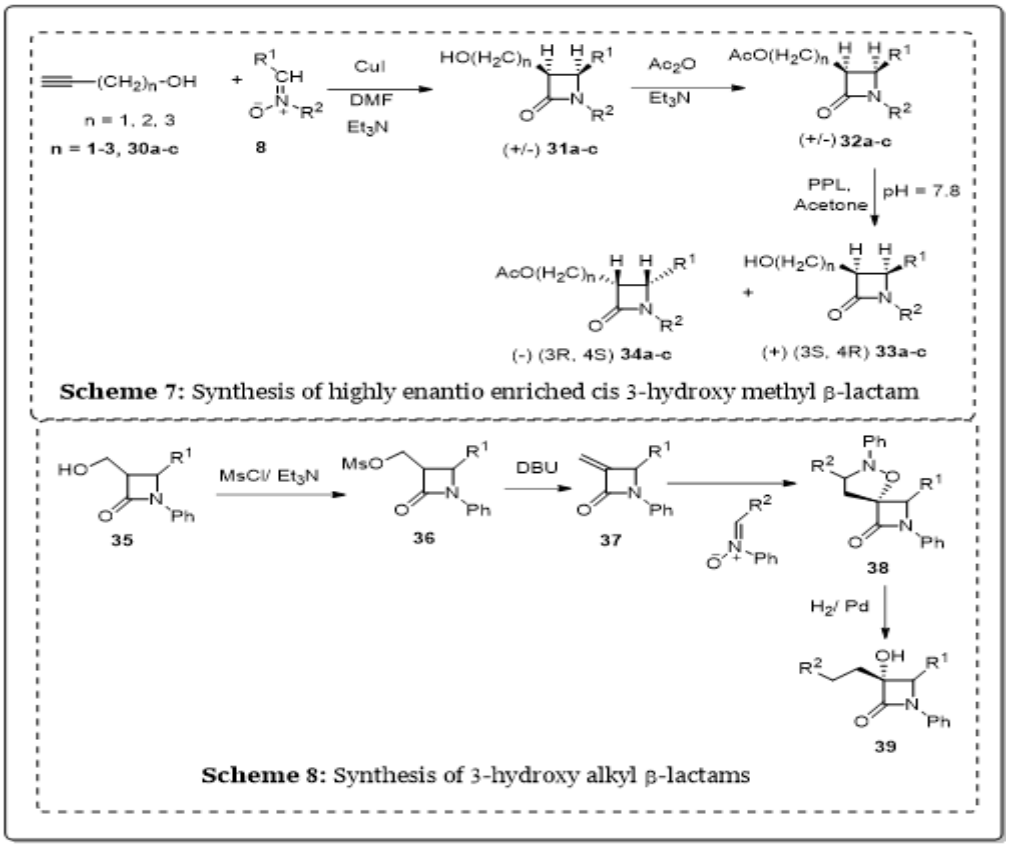
The mechanism proposed in **Scheme 5** is extremely similar to what has been shown in **Scheme 4** for Kinugasa reaction. It may be noted here that whatever may be the actual mechanism, the stereochemical outcome of Kinugasa reaction is dependent upon the initial cycloaddition to form isoxazoline derivative (common for both mechanisms). This addition fixes the configuration at C-4 which, in turn, influences the stereochemistry at C-3. The *cis* β-lactam which is the major diastereomer in most of the cases is generated first. During the reaction, under the basic condition, the *cis* isomer gets converted to the *trans* counterpart through an epimerization process as shown in **Scheme 3**. The extent of the conversion to the *trans* diastereomer depends upon the ease of isomerisation at C-3 under basic condition and on the type of substituent at this position. For example, with ethyl propiolate, because of extreme ease of epimerization, it is only the *trans* isomer that could be isolated. The duration of the reaction is also an important contributor. In 1986 Sandhu *et al*.[13] reported examples where exclusively *trans* product is obtained. The formation of *trans*–4-benzyl-3-phenyl-1-tolylazetidin-2-one from copper (I) phenylacetylide and phenethylidene (N-tolyl) amine-N-oxide in 88% yield is one of those examples. New reports emerged gradually with time and modification of original protocol for the Kinugasa reaction was made. For example, Miura and co-workers (1993 and 1995)[14, 15] reported the Kinugasa reaction between phenyl acetylene **21** and a series of substituted C, N-diarylnitrones represented by **22** as per the conditions mentioned in **Scheme 6.** In this report the yield of the resulting products **23-26** was dependent upon the type of phosphanes or nitrogen containing ligands used.

When the reaction was carried out in absence of ligands or with ligands containing phosphane such as Ph_3P, Bu_3P, dppe, dppp, the *trans* β-lactam **25** was obtained as the only product albeit in poor yield. In presence of nitrogen containing ligands such as pyridine and 1, 10 – phenanthroline, the yield of β-lactams (55 - 71%) significantly increased and both *cis* (**24**) and *trans* (**25**) isomers were obtained in ratio of (*cis*: *trans*) 2:1 and 1:1.2 respectively.



Scheme 6: The first report of asymmetric intermolecular Kinugasa reaction by Miura *et al.*

Over the past few years, our laboratory has also been involved in the synthesis of β-lactams by Kinugasa reaction. In one of the earlier report, [16a] *cis*-3-hydroxy methyl β-lactams were obtained in highly enantio-enriched form by carrying out the reaction between various nitrones **8** and hydroxy alkynes **30a**, followed by acetylation and enzymatic hydrolysis with PPL - pig pancreatic lipase (**Scheme 7**). These β-lactams were finally converted to "3-hydroxy 3-alkyl β-lactams" (**Scheme 8**) *via* a nitrone cycloaddition, [16b] followed by reduction.



Scheme 7: Synthesis of highly enantio enriched cis 3-hydroxy methyl β-lactam

Scheme 8: Synthesis of 3-hydroxy alkyl β-lactams

3. *Asymmetric Kinugasa Reaction*

There are three options to induce asymmetry in the Kinugasa reaction. These are: use a chiral a) nitrone or b) acetylene or c) a ligand designed for chelation to copper (I). The asymmetric induction in all the three instances will be guided by the energy of the diastereomeric transition states generated. Miura was the first to utilize the third strategy for asymmetric Kinugasa reaction with chiral bisoxazoline type ligands (**27-29**).[15] The enantiomeric excess of the β-lactams was dependent upon the various conditions which are reflected in the results shown in **Table 1**.

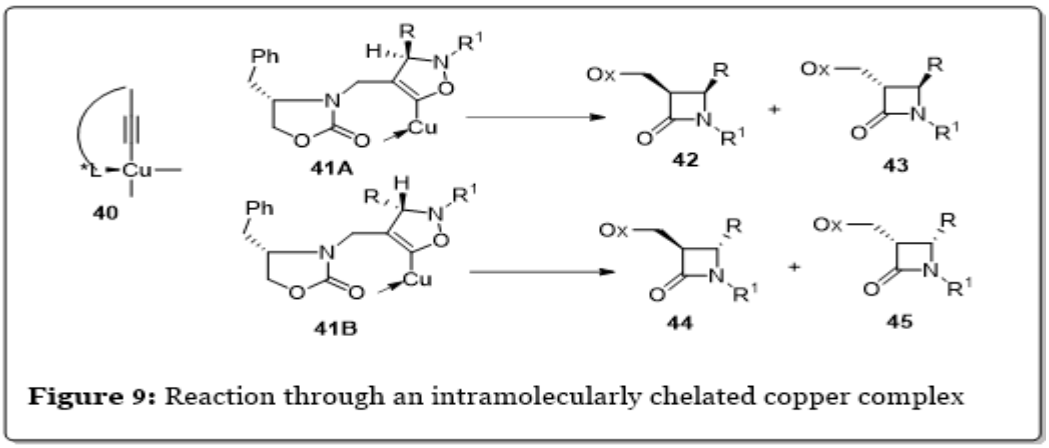


Figure 9: Reaction through an intramolecularly chelated copper complex

It occurred to us that the degree of induction might improve if the ligand is crafted on to one of the components, namely the acetylene so that the reaction would proceed through an

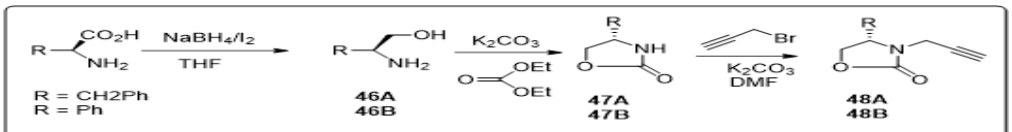
intramolecularly chelated copper complex (as shown in **40, Scheme 9**). Evan's chiral oxazolidinyl acid chloride[17a] has been successfully employed as ketene synthon to bring about a high degree of asymmetric induction in the Staudinger reaction.[17b, c] A similar strategy may be adopted in case of the Kinugasa reaction by using a homochiral *N*-propargyl oxazolidinone. It was hoped that the oxazolidinone side chain would control the approach of the nitrone.

Table 1: Reaction of phenyl acetylene **21** with nitrone **22** in the Presence of Chiral Ligands **27-29**

Entry	Ligand	CuI: Ligand (in mmol)	Time hr	Yield of *trans* β-lactams (%)	*ee* (%)
1	**27**	0.1:0.2	5	5	Not determined
2	**27**	0.1:1	2	45	40
3	**27**	1:1	1	54	68
4	**27**	0.1:0.2	2	50	57
5	**28**	1:1	1	53	67
6	**29**	1:1	2	40	45

The intermediate **41A** having the substituents (benzyl and R) on opposite faces should be of lower energy as compared to intermediate **41B** where they are on the same face. Similar prediction can be extended for the respective transition states. Thus, there will be a preference for the chirality at C-4 of the resulting isoxazoline. This, in turn, will fix the chirality at C-3 for the *cis* and the *trans* azetidinone; the latter has already been shown to originate from the former, *via* epimerization. [11]

(4*S*)-benzyl and phenyl substituted propargyl–3-oxazolidones (**48A** and **48B** respectively) were chosen as the chiral ligand-tethered acetylene component for our work. (*S*)-Phenylalanine and (S)-phenyl glycine served as the starting materials to synthesize these compounds (**Scheme 10).** These N-propargyl oxazolidones, **48A** and **48B** were stable only at 0-5 °C. They decompose slowly even at that temperature and hence were immediately used after synthesis for Kinugasa reaction. On reacting with various nitrones **49A-49D** in presence of CuI and Et_3N, substituted propargyl-3-oxazolidones **48A** and **48B** yielded β-lactams **50A-G** and **51A-G** (**Scheme 11**) in moderate yields.[18]

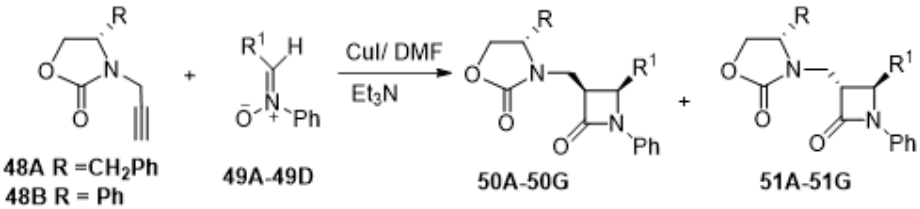


Scheme 10: Synthesis of 4-substituted N-propargyl oxazolidones

The ^1H NMR spectra of the crude reaction mixture showed the presence of one *cis* and one *trans* diastereomer which were easily separated by column chromatography. The purity of the diastereomers was revealed by their ^1H and ^{13}C NMR spectra with only one set of signals being present, even in the presence of chiral shift reagent [Eu(fod)$_3$]. The purity of the diastereomers was confirmed by HPLC analysis. The data provided in the **Table 2,** showed that these reactions proceeded in good and acceptable yields and exhibited excellent levels of stereochemical control. They have the added advantage of providing greater than 95% asymmetric induction (estimated by HPLC and NMR) in both the *cis* and *trans* product domain.

Table 2: Cycloaddition of **48A-48B** nitrones **49A-49D**

Acetylene Component	Nitrone	Ratio of *trans* and *cis*	Combined Yield (%)
48A	**49A**	3:2	65
48A	**49B**	5:4	63
48A	**49C**	5:4	65
48A	**49D**	5:3	70
48B	**49A**	3:1	65
48B	**49B**	3:1	62
48B	**49C**	3:1	63



For **49A, 50A, 51A** R = CH_2Ph, R^1 = Ph

For **49B, 50B, 51B** R = CH_2Ph, R^1= furan

For **49C, 50C, 51C** R = CH_2Ph, R^1 = thiophene

For **49D, 50D, 51D** R = CH_2Ph, R^1 = p-OMe Phenyl

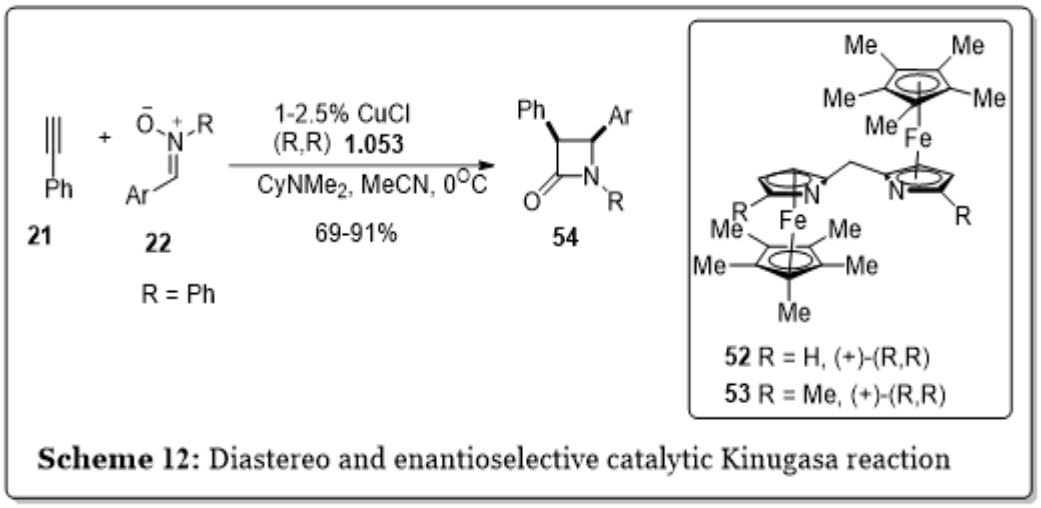
For **50E, 51E** R = Ph, R^1 = Ph

For **50F, 51F** R = Ph, R^1 = furan

For **50G, 51G** R = Ph, R^1 = thiophene

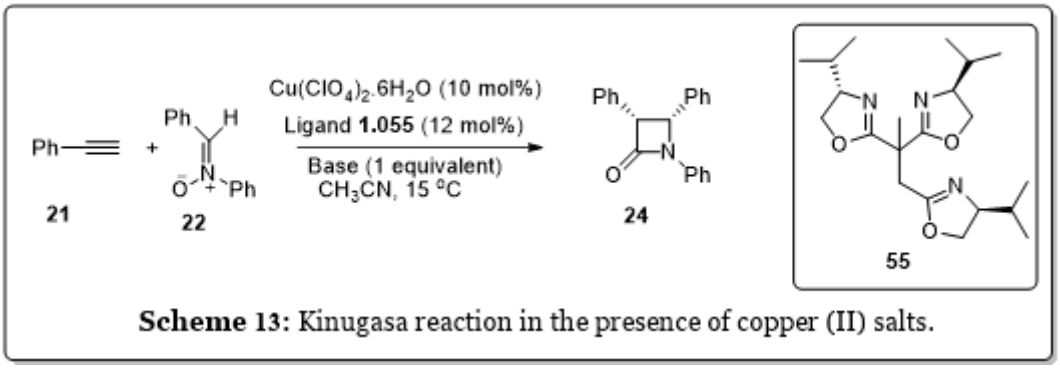
Scheme 11: Synthesis of chiral auxiliary based β-lactams

In 2002 Lo and Fu[19] reported the first completely diastereo- and enantioselective catalytic Kinugasa reaction, using the chiral-ligand strategy. This was possible with the sterically hindered base N, N-dimethylcyclohexylamine and new C_2-symmetric planar-chiral bis(azaferrocene) ligands. Under Miura's conditions, the coupling of phenylacetylene (**21**) with N,α-diphenylnitrone (**22**, Ar=R=Ph) in the presence of **52** and catalytic amounts of copper chloride led to moderate stereoselection. With catalyst **53**, the formation of β-lactams **54** (**Scheme 12**) proceeded with excellent *cis* diastereoselectivity (95:5) and good *ee* (from 69 to 91%). The more electron-rich the nitrone was, the higher was the enantioselectivity; the best results were obtained for the p-anisyl derivatives **22** (Ar = p-MeOPh).



Scheme 12: Diastereo and enantioselective catalytic Kinugasa reaction

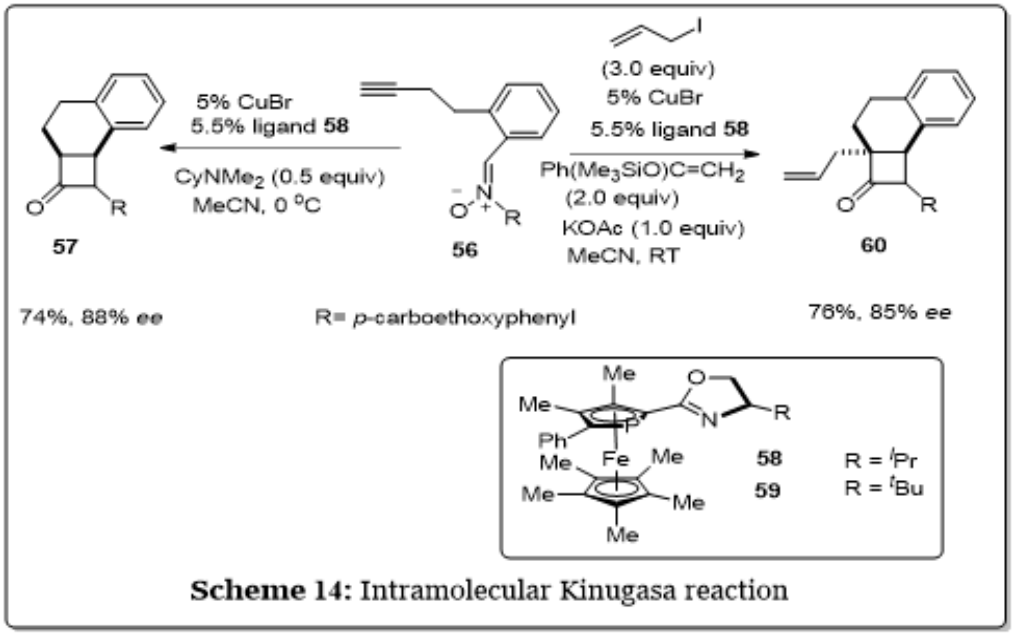
Very recently, Tang *et al.*[20a, b] reported that the chiral tris(oxazoline) **55** in the presence of $Cu(ClO_4)_2 \cdot 6H_2O$ catalyzed the Kinugasa reaction between terminal alkynes **21** and nitrones **22**, giving high *cis* diastereoselection and good enantioselectivity (55–85% *ee*) (**Scheme 13**). Particular emphasis was placed on the effect of the base on the asymmetric induction; they found that secondary bases, particularly dicyclohexylamine, gave better results than primary or tertiary amines. They also performed the Kinugasa reaction for the first time in the presence of copper (II) salts, which was an interesting variation of the previous protocols.



Scheme 13: Kinugasa reaction in the presence of copper (II) salts.

4. *Intramolecular Kinugasa Reaction*

Intramolecular asymmetric Kinugasa reaction was first reported by Shintani and Fu in 2003.[21] In this report the alkynyl nitrone **56** as the substrate, under the previously documented experimental conditions and in presence of catalysts **52** and **53** generated the expected adduct **57** in poor to modest stereoselectivity (**Scheme 14**).

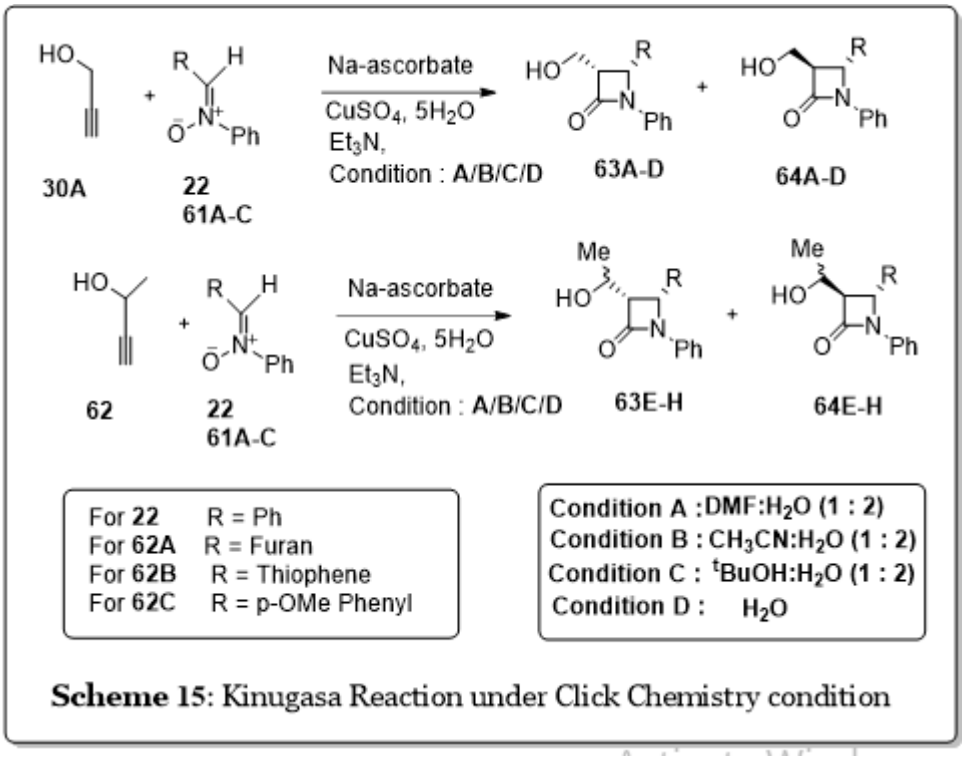


Scheme 14: Intramolecular Kinugasa reaction

The use of planar-chiral phosphaferrocene-oxazolines **58** and **59** notably improved the enantioselectivity. In addition to these interesting observations, the authors were able to trap the *in situ*-formed intermediate copper enolate, postulated in the mechanism for the Kinugasa reaction. This intermediate was trapped by doing the reaction in presence of suitable electrophiles (like allyl iodide) when compound **56** was obtained (**Scheme 14**).

5. *Kinugasa Reactions under Click Chemistry Condition*

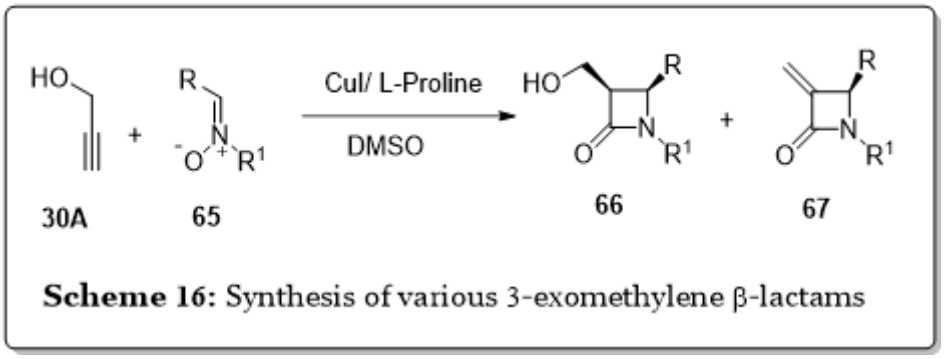
Various monocyclic β-lactams, both *cis* and *trans*, have been successfully prepared *via* Kinugasa reaction mimicking the Click Chemistry conditions[22] (**Scheme 15**). The reaction worked even in presence of water with a low catalyst loading of 10 mole %. The reaction gave almost similar result if $CuSO_4$ is replaced by Cu $(OAc)_2$. The reaction did not work in the absence of L-ascorbate thus ruling out the involvement of Cu (II) in Kinugasa reaction. Lowering the amount of $CuSO_4$ to less than 1 eq. produced similar result both in terms of yield and selectivity. The amount of catalyst can be lowered up to 10 mol% without affecting the results. Further lowering caused reduction in yield and the reaction became sluggish. Regarding the choice of solvent, the reaction worked well even if only water was used as the solvent; the diastereoselection, however, remained the same.[23] Terminal acetylenes, which are extremely non polar like phenyl acetylene, however, failed to produce any β-lactam under these conditions.



Scheme 15: Kinugasa Reaction under Click Chemistry condition

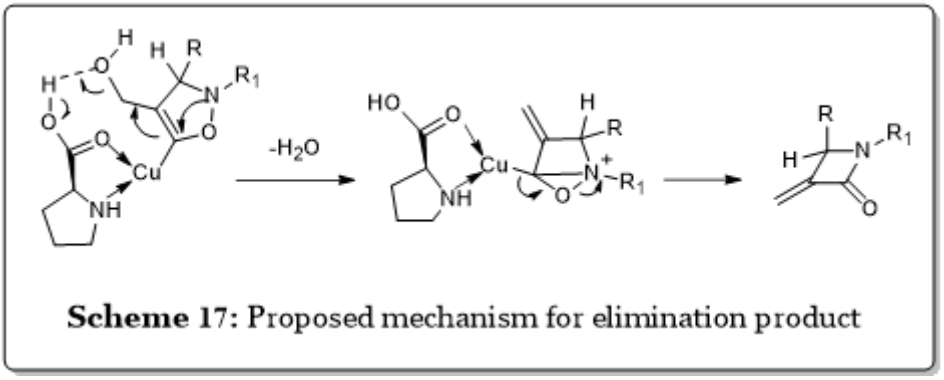
6. *Proline mediated Kinugasa Reaction*

Considering the importance of α-alkylidene-β-lactams in medicinal and synthetic chemistry,[24] L-proline mediated one pot synthesis of these compounds *via* Kinugasa reaction was developed. Propargyl alcohol was used as the acetylene component and the reaction was carried out with various nitrones in presence of CuI and L-proline in DMSO at room temperature (**Scheme 16**). The reaction yielded the 3-exomethylene-β-lactams as the major product (70-75%) and *cis* 3-methyl hydroxy-β-lactams as the minor product (8-10%).



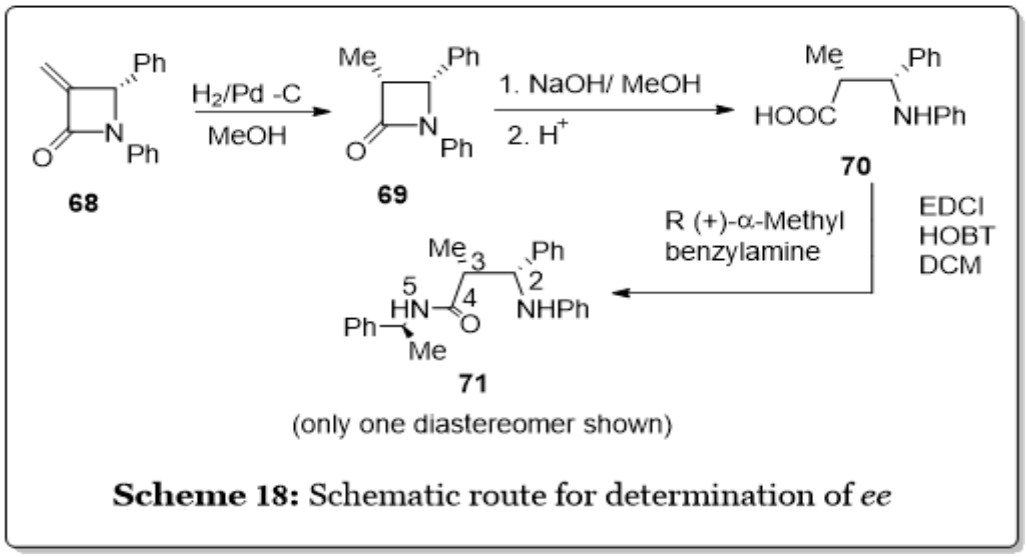
Scheme 16: Synthesis of various 3-exomethylene β-lactams

The proposed mechanistic pathway for the formation of elimination product is shown in **Scheme 17**.



Scheme 17: Proposed mechanism for elimination product

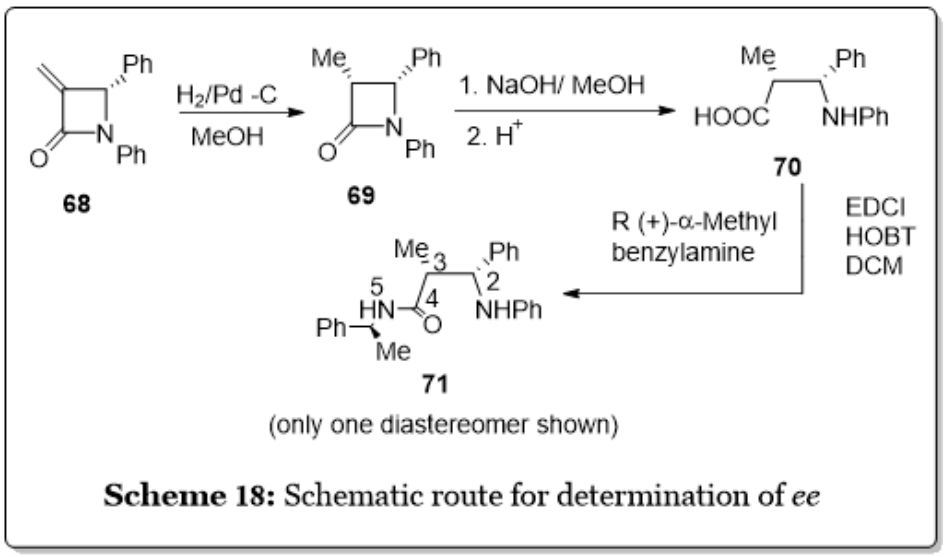
The elimination required the presence of amphoteric systems as is present in proline. Other amino acids also induce elimination but with lower efficiency. Bases like piperidine or pyrrolidine could not induce any elimination. Chiral HPLC was unsuitable for determination of enantiomeric excess of the 3-exo methylene-β-lactams. Finally we have been able to determine the enantiomeric excess of the 3-exo methylene products by a three-step protocol (**Scheme 18**). The *ee* (2-15%) was, however, poor.[25]



Scheme 18: Schematic route for determination of *ee*

7. *Kinugasa reaction in the synthesis of peptidomimetics*

Consideration of the fact that β-turn based pharmacophore design[26] has become a central topic in bioorganic chemistry led us to design and synthesize an efficient peptidyl β-lactam **80** and **81** and study their conformational preference. The synthesis of the peptides relied upon the availability of the 3-pyroglutamylmethyl β-lactam in *cis* and *trans* forms, preferably enanatiomerically pure. Kinugasa reaction was again utilized here to prepare these compounds using propargyl ethyl pyroglutamate and diphenyl nitrone in presence of CuI and Et_3N in CH_3CN solution (**Scheme 19**). Interestingly, the reaction produced three diastereomers: one *trans* isomer **73** and a pair of *cis* isomers **74** and **75**. It appeared that only one of the *cis* isomer **75** has epimerized to the *trans* compound during the reaction. The other *cis* isomer **74** was configurationally more stable and was resistant to epimerization. The presence of intramolecular hydrogen bonding was determined from the temperature coefficients (**Table 3**) of chemical shifts of the two NH protons of both the tripeptides. The data showed that in the *trans* peptide **80** the temperature coefficient of the chemical shift of NH of glycine was the lowest and was close to the Kessler limit[27] of 3 ppb suggesting strong intramolecular H-bonding.



Scheme 18: Schematic route for determination of *ee*

For both the *cis* tripeptides **81** and **82**, the temperature coefficients of chemical shifts for all the NHs were above 5.0 ppb, which indicated the absence of a definite turn motif in these Systems.[28] Thus, it seemed that while a β-turn like-conformation was preferred in the *trans* peptide **80**, no such preferences could be seen in the *cis* peptides **81** or **82.** Hence it was concluded that the stereochemistry of the β-lactam ring played, a key role in controlling the conformation of the peptides. Absolute stereochemistry of the *trans* β-lactam **76** was confirmed by X-ray crystallography analysis. For the *cis* β-lactams, the absolute configurations were assigned on the basis of CD-spectroscopy.[28]

Table 3: NMR Temperature coefficients of NH chemical shifts in DMSO-d_6[a]

Peptide	NH (glycine)	NH (phenylalanine)
80	3.4	5.6
81	5.8	6.1
82	5.4	5.6

8. *Conclusions*

Since its discovery in 1972, Kinugasa reaction has offered an attractive method for the synthesis of various β-lactam derivatives in both *cis* and *trans* configuration in moderate to good yields. The scope of the reaction has widened recently by various reports of asymmetric versions and the synthesis of delicate systems like □-lactam fused enediynes, a promising class of antitumor agents. More developments are expected in near future.

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