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Review Article

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Recent advances in the synthesis of *β*-lactum derivatives using nitrone cycloaddition reactions

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ABSTRACT

Synthesis of β-lactums are always most attractive and challenging to a synthetic organic chemist. Various routes for the synthesis of β-lactum derivatives have been reported in the literature. In this review, our endeavour is to accumulate few important reports on the synthesis of β-lactums and their further applications so as to assist researchers who intent to pursue research in this field.

Keywords: *β*-lactum, Kinugasa reaction, catalysts, biological activity

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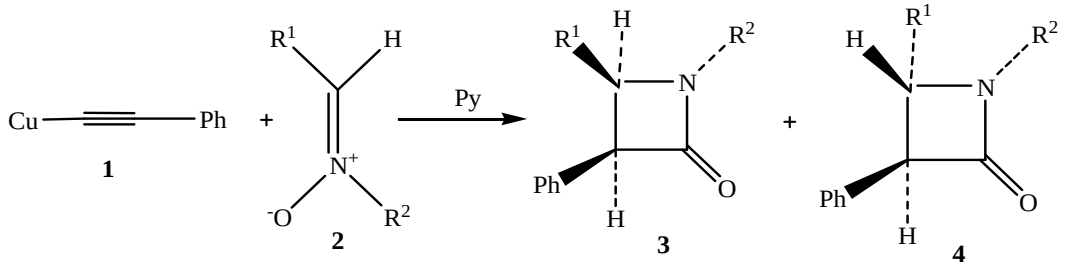
INTRODUCTION

The *β*-lactums are one of the best known and extensively investigated heterocyclic ring systems as a result of both their biological activity as antibiotics [1-5] and their utility as synthetic intermediates [6]. Among the different synthetic approaches for the preparation of *β*-lactums [1-5], the Kinugasa reaction [7] has been largely employed in the current practice of *β*-lactum synthesis in organic chemistry. Intensive research has generated numerous methods of synthesizing the *β* -lactam skeleton [8]. Commonly, the lactam ring is formed through either ketene-imine cyclizations [9] (the Staudinger reaction) or ester enolate imine condensations [10-12] (the Gilman-Speeter reaction).

REVIEW

Nitrone cycloaddition reactions are found to be versatile method for the synthesis of a wide variety of *β*-lactam derivatives (the Kinugasa reaction). A number of noteworthy strategies have been described, almost all of which rely upon the generation of chiral, nonracemic precursors, followed by formation of the four-membered ring [1-5; 6]. In its first description [13] the Kinugasa reaction involved the reaction of copper (I) phenylacetylide with nitrones to produce *β*-lactams (**Scheme 1**). The reaction was performed in anhydrous pyridine at room temperature under nitrogen atmosphere and with short reaction times (from 30 min to 1 h); after hydrolysis and workup, the exclusively *cis* products were obtained in good yields (from 51.2 to 60.2%). Interestingly, the use of copper (I) phenylacetylide as the reagent was critical, as the reaction of alkynes with nitrones affords pyrrolinediones or isoxazolines [13].

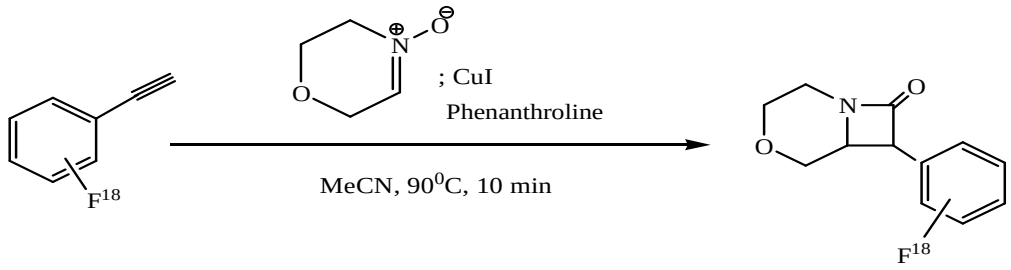


4a :R^1= Ph, $OMeC_6H_4$, O-ClC_6H_4

4b : R^2= Ph, O-ClC_6H_4

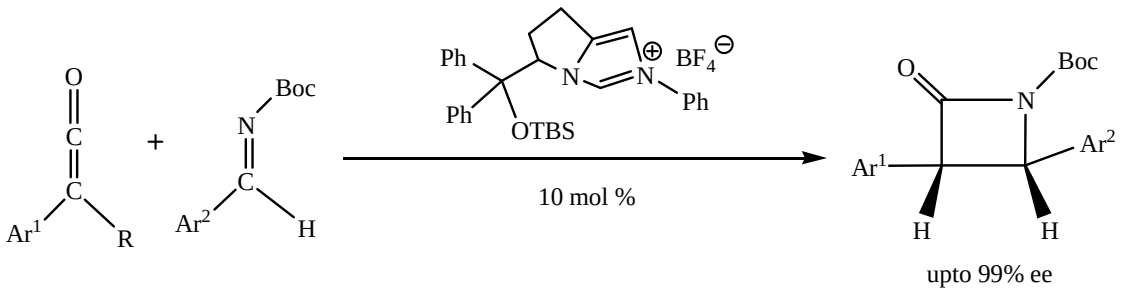
Scheme 1. Synthesis of beta lactums by Kinusaga reaction

Recently, some of the contributions in the synthesis of β-lactum have attracted synthetic chemists for their novelty [14-16]. Neumaier et al [14] have shown synthesis of ^{18}F labeled β-lactums using Kinugasa reaction (**Scheme 2**).



Scheme 2. Synthesis of labeled bicyclic β-lactums using Kinugasa reaction

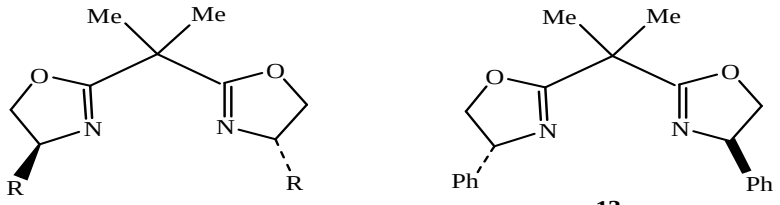
Zhang et al [15] have shown bifunctional *N*-heterocyclic carbine catalyzed highly enantioselective synthesis of spirocyclic β-lactums (**Scheme 3**). .



Scheme 3. *N*-heterocyclic carbene catalysed cycloaddition of ketenes with aldimines

Rominger et al [16] have shown recently an efficient approach for the synthesis of functionalized β-lactums through a sequential cyclization reaction. Diversity oriented synthesis, good to excellent yields easy workup and short reaction times are the advantages of this procedure

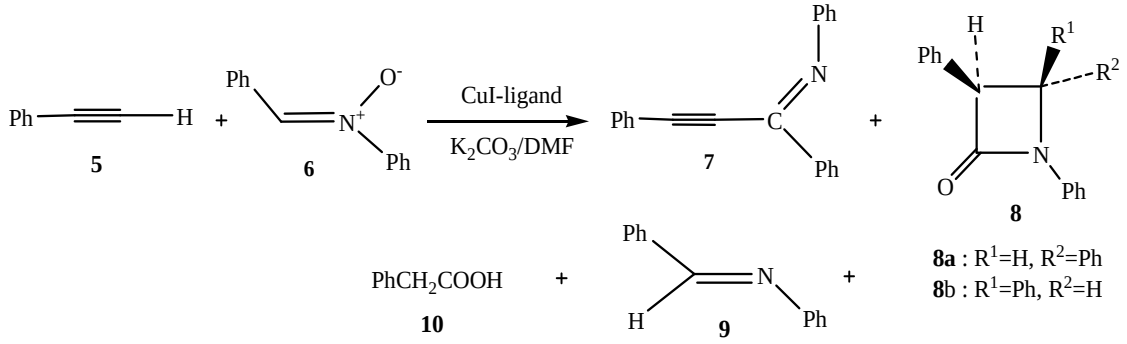
In 1993 in a preliminary communication and in 1995 in a full paper, Miura and co-workers reported [17,18] an interesting modification in the original protocol for the Kinugasa reaction based on the reaction of phenylacetylene (**5**) with a series of C, N-diarylnitrones (**6**) in the presence of catalytic amounts of copper iodide and potassium carbonate. In an extension of these results, Miura and colleagues described the first examples of the asymmetric intermolecular Kinugasa reaction with chiral ligands [17]. For this purpose bisoxazolinetype ligands (**11–13**) were selected.



11 : R = iPr
12 : R = tBu

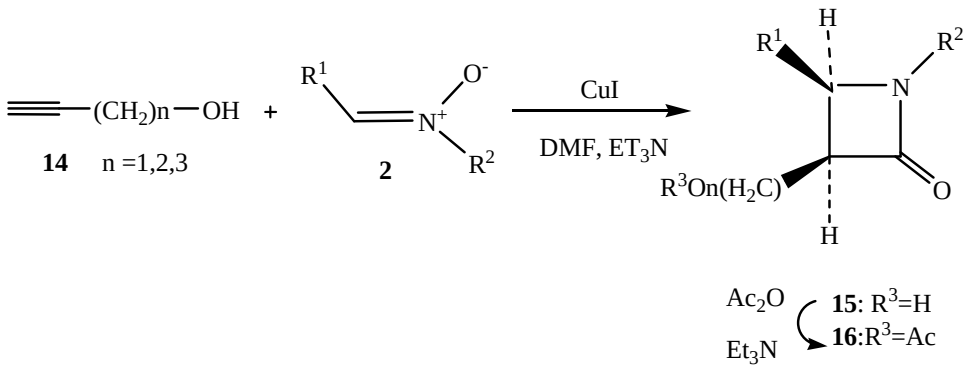
13

With stoichiometric amounts of compound **11**, the reaction of alkyne **5** with nitrone **6** (**Scheme 4**) provided *β*-lactams 8a,b in 45% yield and in a 35:65 ratio; each pure isomer showed a 40% *ee*; increasing the amount of CuI to 1 mmol resulted in 68% *ee*. Chiral ligands **12** and **13** generated similar products with enantiomeric excesses of 67% and 45%, respectively. After some experimentation it was found that for the same reaction, the slow addition of the phenylacetylene (**5)** to a mixture of nitrone **6**, CuI (0.1 mmol), and **11** (0.2 mmol) afforded a selectivity of 57% *ee*. When catalysts **12** and **13** were used under these conditions, copper (I) phenylacetylide precipitated preventing further reaction.

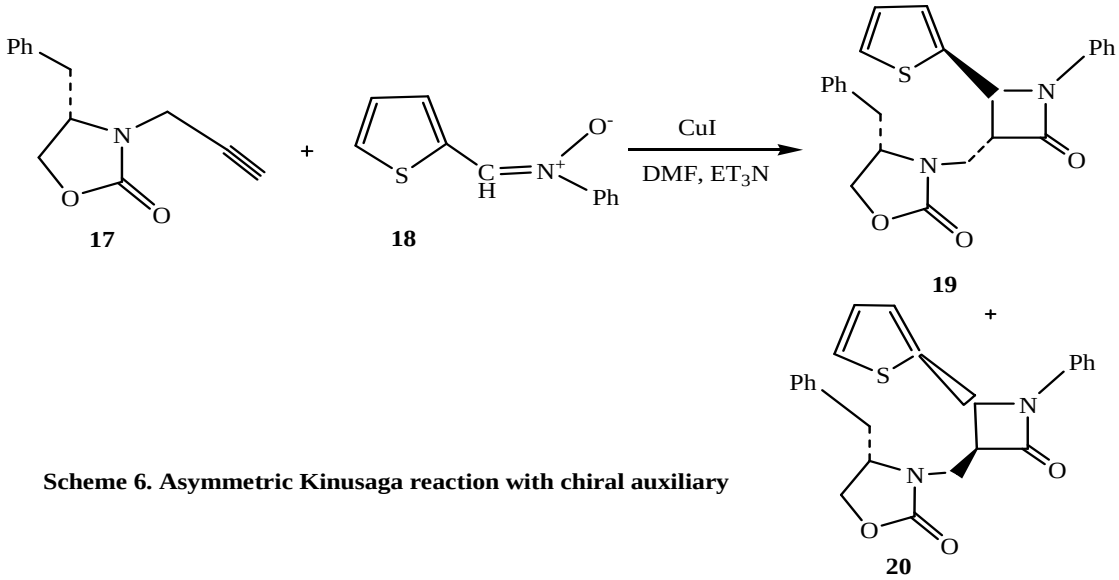


Scheme 4. The Kinusaga reaction according to Miura et al

In 1997 and 1998 in their first two contributions in this area Basak et al. described the synthesis of the cis-*β*-lactams **16** by the Kinugasa reaction of the corresponding nitrones **2** and alkynyl alcohols **14**, followed by acetylation of the intermediate alcohols **15** (**Scheme 5**) [19,20]. Compound **16** was then hydrolyzed with pig pancreatic lipase (PPL) to provide enantiomerically pure 2-azetidinone compounds. More recently, Basak et al. reported an asymmetric version of the Kinugasa reaction using Evans's oxazolidinone as a chiral auxiliary [21]. Accordingly, precursor **17** was synthesized and submitted to reaction with nitrone **18**, providing mixtures of *trans*- and *cis β*-lactams (**19** and **20**, **Scheme 6**), both in enantiopure form and with a stereoselectivity in the range of 95%. The absolute configuration at these centers was assigned by X-ray structure analysis of compound **19** (**Scheme 4**).



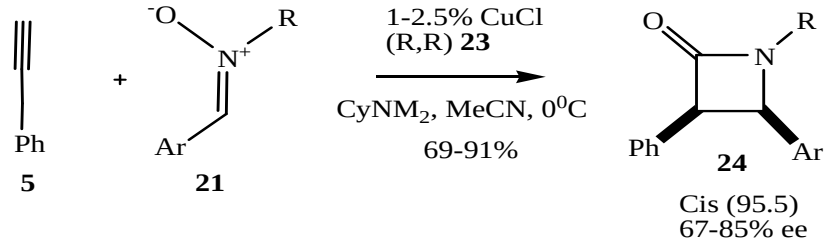
Scheme 5. The Kinusaga reaction as reported by Basak et al



Scheme 6. Asymmetric Kinusaga reaction with chiral auxiliary

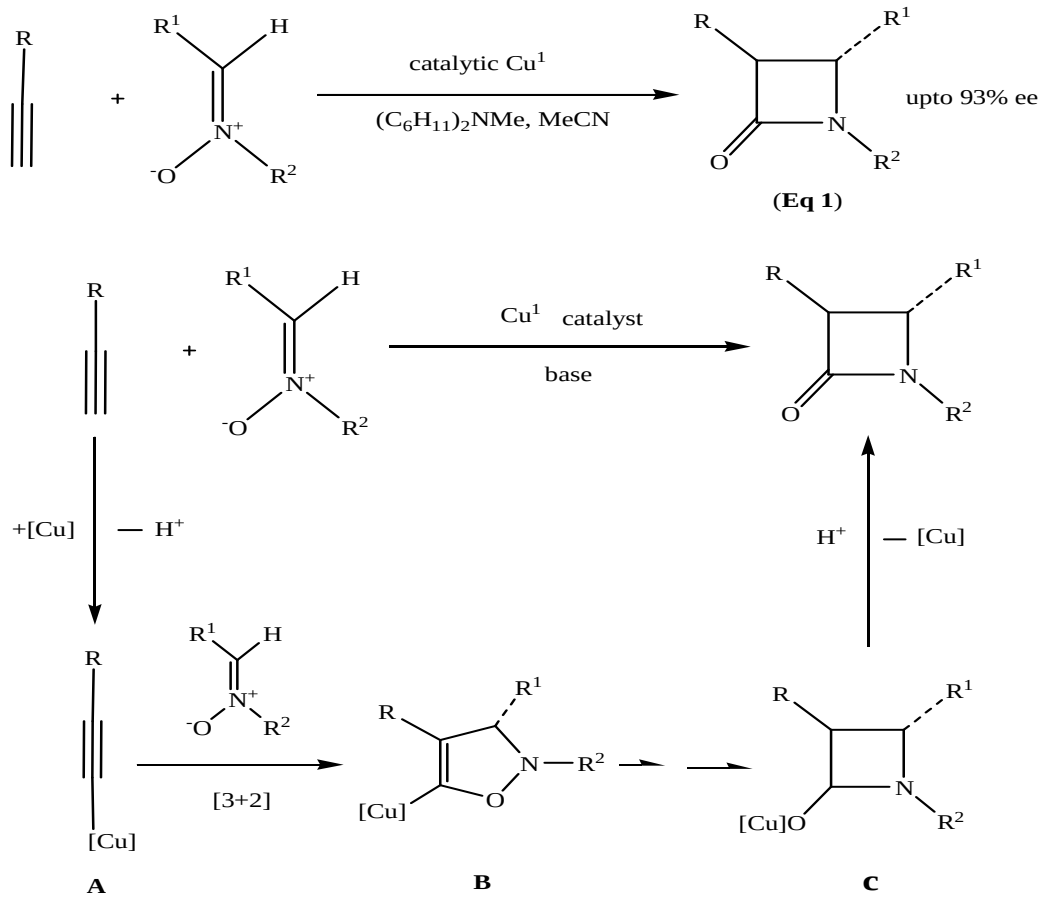
Finally, they demonstrated, as had been previously proposed [19,20], that the *cis* isomers isomerize to the *trans* isomers upon treatment with base (nBuLi) at low temperature. However, they did not attempt to remove the chiral auxiliary from the intermediates to give the free, enantiomerically pure *β*-lactams.

In 2002 Lo and Fu reported the first completely diastereo- and enantioselective catalytic Kinugasa reaction, using the chiral-ligand strategy [22]. 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 [23], the coupling of phenylacetylene (**5**) with *N*,α-diphenylnitrone (**21**, Ar=R=Ph) and catalytic amounts of copper chloride led to moderate stereoselection. With catalyst **23** the formation of *β*-lactams **24** (**Scheme 7**) proceeded with excellent *cis* diastereoselectivity (95:5) and good *ee* (from 67 to 85%).



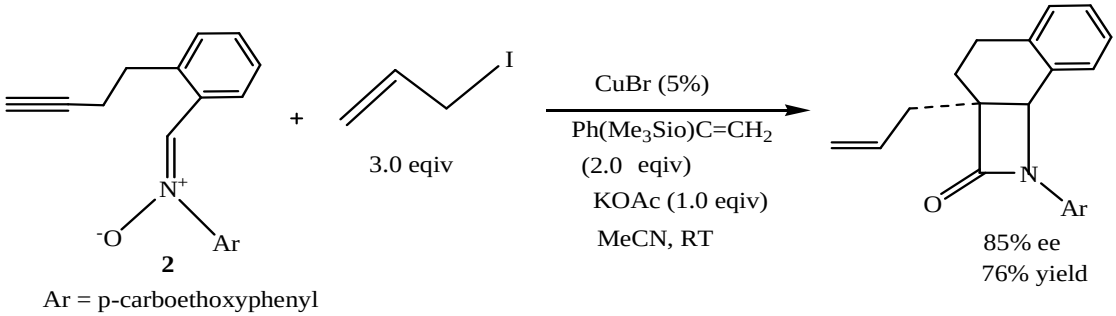
Scheme 7. Asymmetric Kinugasa reaction according to Lo and Fu. Cy=cyclohexyl.

Based on the pioneering work of Kinugasa et al [24], Miura et al [25], and others [26,27], Ryo Shintani and Gregory C. Fu described a copper/ bisazaferrocene-catalyzed method for the asymmetric coupling of alkynes with nitrones (the Kinugasa reaction; [**Scheme 8**). This mild approach to the generation generation of *β*-lactams is very attractive owing to its convergence, its high functional-group tolerance, and the ready availability and stability of alkynes and nitrones. Shintani et al also developed intramolecular Kinugasa reactions, ideally with a chiral catalyst, with a view to preparing enantioenriched bi- and polycyclic *β*-lactams. They have reported a copper/phosphaferrocene–oxazoline catalyst mediates asymmetric intramolecular Kinugasa reactions to produce two new rings with very good stereoselectivity. Furthermore, they establish one of the presumed intermediates in the catalytic cycle (**C** in **Scheme 8**) can be intercepted with an electrophile to generate an additional C_C bond and a quaternary stereocenter.



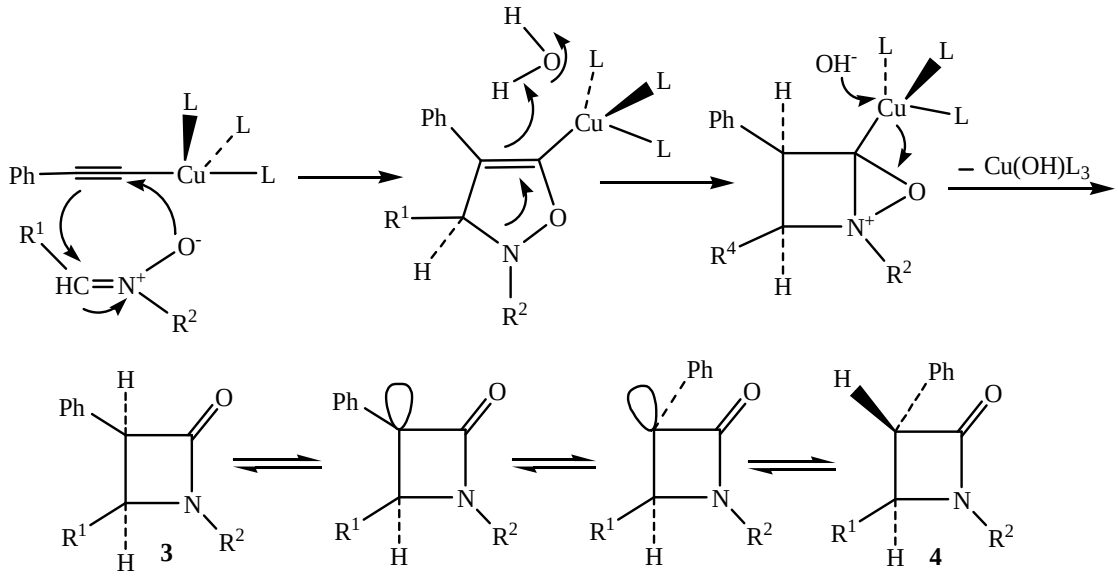
Scheme 8. Outline of a possible mechanism for the Kinugasa reaction

The proposed mechanism for the Kinugasa reaction is illustrated in **Scheme 8** [28–31]. It is believed that the terminal alkyne is converted into copper acetylide A in the presence of CuI and a base e.g., $(C_6H_{11})_2NMe$) [6], and that A participates in a [3+2] dipolar cycloaddition with the nitrone. The resulting heterocycle B then rearranges to afford the conjugate base of a *β*-lactam (enolate C). Protonation (e.g., by [(C_6H_{11})2NHMe]+) furnishes the desired product and releases the copper catalyst. It has been observed from the study that the utility of the Kinugasa reaction would be further enhanced if it is possible to intercept intermediate C by adding an electrophile to the reaction mixture. Shintani et al also demonstrated that an intramolecular Kinugasa reaction can be used to prepare fused tricyclic ring systems efficiently with very good levels of enantioselectivity in the presence of a planar-chiral Cu/phosphaferrocene–oxazoline catalyst (**Scheme 9**).



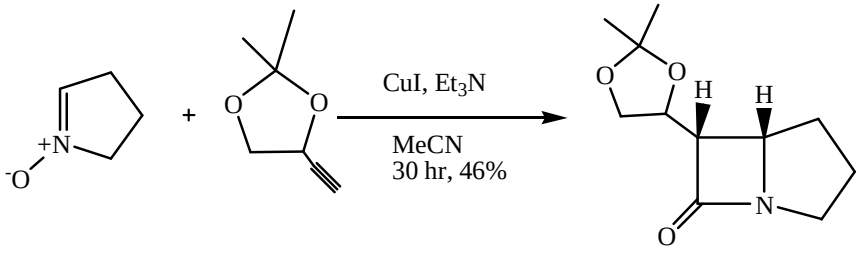
Scheme 9

In 1976, Ding and Irwin reported on the scope and limitation of the Kinugasa reaction in a full paper [32], showing that under the general experimental conditions [28], mixtures of *cis* and *trans*-*β*-lactams were always obtained in different ratios (from 1:1 to 12:1), the cis- *β*- lactam **3** being the major diastereomer in most cases; the extent of formation of trans-*β*-lactam 4 (**Scheme 10**) seemed related to the ease of isomerization at C-3 under the basic conditions, and ultimately to the type of substituents at this position. These authors also proposed the first mechanism for the Kinugasa reaction (**Scheme 9**), which is still accepted today. In 1986, overlooking Kinugasa's seminal report Sandhu and colleagues described the reaction of copper (I) phenylacetylide with benzoyl-*N*-tolylnitrone in pyridine, rendering only one compound, the trans-1-tolyl-3-phenyl-4-benzoylazetidin-2-one, in 88% yield [30].



Scheme 10. Mechanism for the Kinusaga reaction proposed by Ding and Irwin

Recently reported diastereoselective synthesis of *β*-lactum derivatives was carried out by Chmielewski and coworkers where minor product of the mixture of diastereomer was not isolated [33].



diastereomeric ratio : 90:10
(minor pdt was not isolated)

Scheme 11

In a recently published work, we have reported that α-chloro nitrones can also be used as a precursor for the synthesis various *β*-lactum derivatives [34]. Further work is in progress.

CONCLUSION

In summary, the Kinugasa reaction is a simple, but efficient protocol for the synthesis of *β*-lactums in racemic or enantiomerically pure form, with attractive features that include ready availability of the starting material (alkynes and nitrones), convergence, and high functional-group tolerance. The recently described new aspects in the Kinugasa reaction nicely complement the number of methods known and published for the synthesis of enantiomerically pure β-lactams [4].

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