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An asymmetric synthesis of β-lactams: on the use of chiral oxazolidones in the Kinugasa reaction

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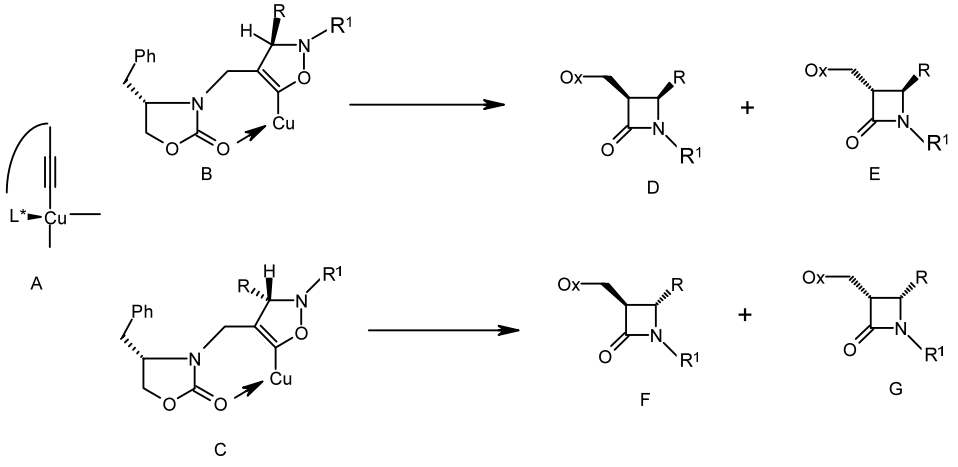
Abstract—Enantiopure *cis* and *trans* β-lactams **3a–e** and **4a–e**, respectively, have been synthesized via cycloaddition between chiral oxazolidinyl propynes **1a–b** and nitrones **2a–d**, in the presence of cuprous iodide (the Kinugasa reaction). © 2002 Published by Elsevier Science Ltd.

Although first synthesized by Staudinger[1] way back in 1907, β-lactams as a class acquired importance only after it was established that penicillin contains this unit as a unique structural feature. Since then, several other naturally occurring β-lactams have been isolated and synthesized.[2] Apart from their antibacterial properties, β-lactams also show biological activities that include inhibition of cholesterol absorption[3] and human leukocyte elastase (HLE).[4] More recently, β-lactams have been recognized as useful chiral starting materials for the synthesis of natural and unnatural products.[5] Enantiomerically pure β-lactams have been shown to be versatile intermediates for the synthesis of aromatic amino acids, oligopeptides and azetidines.[6] The use of monocyclic β-lactams as a synthon for the synthesis of the side chain of taxol[7] has solved a challenging problem in the synthesis of taxol from baccatin. Thus any new synthesis that produces homochiral β-lactams is important in its own right and hence, not surprisingly, the interest in β-lactam synthesis continues unabated and several methods have been developed recently, culminating in stereospecific syntheses of β-lactams with requisite functionality.[8] The most important of these methods is obviously the ketene–imine cycloaddition (the Staudinger reaction), which is versatile because of the availability of a wide range of imines and ketenes.[9] Several asymmetric syntheses via ketene–imine cycloadditions are known.[10] On the other hand, the asymmetric version of the Kinugasa reaction,[11] which involves the cycloaddition between an in situ



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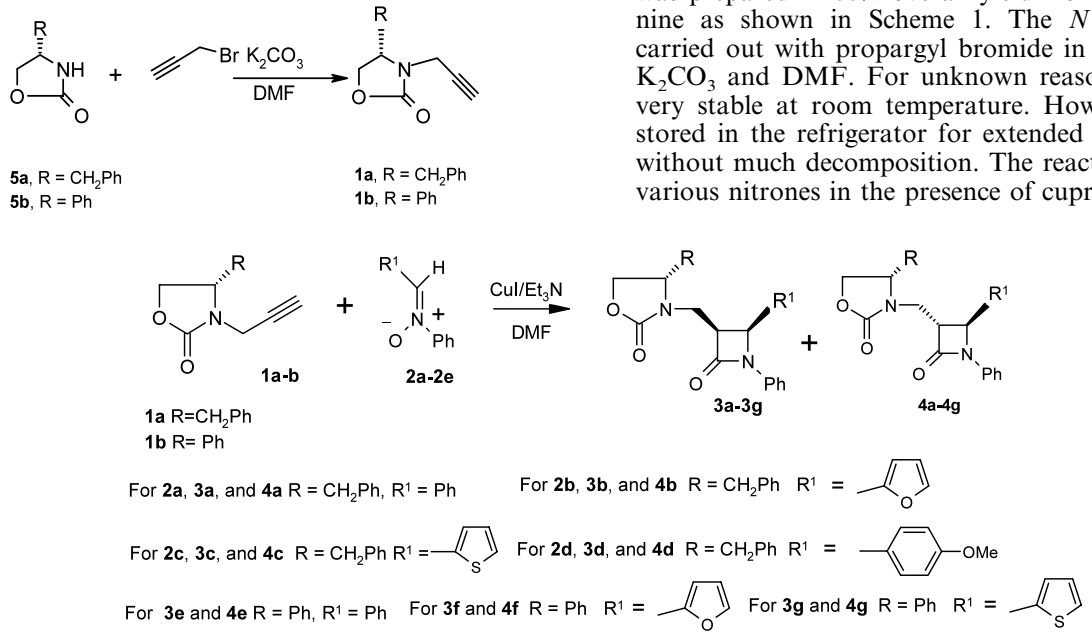
generated cuprous acetylide and a nitrone leading to a β-lactam (usually a mixture of *cis* and *trans*) has not been very successful. Miura et al.[12] achieved an enantiomeric excess of 40–60% by employing a C_2-symmetric oxazoline as a chiral ligand for copper. In this paper, we report a chiral auxiliary based approach to the Kinugasa reaction that proceeds with high enantiospecificity.

To induce asymmetry in the Kinugasa reaction, there are three options: use a chiral (a) nitrone or (b) acetylene or (c) a ligand designed for chelation to copper. All these three approaches rely on the generation of diastereomeric transition states that differ in energy by a substantial amount so as to effect a high degree of asymmetric induction. Miura's approach of using an external chiral ligand resulted in mixed success. 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 proceeds through an intramolecularly chelated copper complex (as shown in **A**).

Evan's chiral oxazolidinyl acid chloride[10a] has been employed as a ketene synthon to bring about a high degree of asymmetric induction in the Staudinger reaction. A similar strategy may be adopted in the case of the Kinugasa reaction by using a homochiral *N*-propargyl oxazolidinone. It was hoped that the oxazolidinone side chain would then control the approach of the nitrone. Intermediate B having the substituents (benzyl and R) on opposite faces should be of lower energy as compared to intermediate C where the substituents are on the same face. Thus there will be a preference for the chirality at C-4 of the resulting isooxazoline. This, in turn, will fix the chirality at C-3 of the *cis* and the *trans* azetidinone; the latter has already been shown[13] to originate from the *cis* diastereomer, via epimerization.

The requisite (4*S*)-benzyl-3-propargyl oxazolidone **1a** was prepared in 60% overall yield from (*S*)-phenylalanine as shown in Scheme 1. The *N*-alkylation was carried out with propargyl bromide in the presence of K_2CO_3 and DMF. For unknown reasons, **1a** was not very stable at room temperature. However, it can be stored in the refrigerator for extended periods of time without much decomposition. The reactions of **1a** with various nitrones in the presence of cuprous iodide were



Scheme 1.

Table 1. Cycloaddition of **1a**–**b** with nitrones (**2a**–**d**)

Acetylene component	Nitrone	Ratio of *trans* and *cis* β-lactams	Combined yield (%)	Compound no./mp/specific rotation[a] of *cis* β-lactams	Compound no./mp/specific rotation[a] of *trans* β-lactams
1a	**2a**	3:2	65	**3a**/160–162°C/(+) 131	**4a**/158–160°C/(−) 37.3
1a	**2b**	5:4	63	**3b**/144–145°C/(+) 54.4	**4b**/95–98°C/(−) 65.1
1a	**2c**	5:4	65	**3c**/161–163°C/(+) 98.6	**4c**/120–122°C/(−) 23.5
1a	**2d**	5:3	70	**3d**/140–142°C/(+) 55.9	**4d**/55–57°C/(−) 7.9
1b	**2a**	3:1	65	**3e**/210–212°C/(+) 195.8	**4e**/192–194°C/(−) 45.7
1b	**2b**	3:1	62	**3f**/192–193°C/(+) 181.7	**4f**/185–186°C/(−) 43.1
1b	**2c**	3:1	63	**3g**/165–166°C/(+) 181.7	**4g**/202–203°C/(−) 38.5

[a] Rotations were recorded in $CHCl_3$ at 27°C. General procedure: To a solution of **1a** in DMF under argon at 0°C, triethylamine (1 equiv.) was added and the mixture stirred for 30 min. Cuprous iodide (1 equiv.) was added and the solution was stirred for another 5 min at 0°C after which a DMF solution of the nitrone (0.75 equiv.) was added slowly over 5 min. After stirring for another 30 min at 0°C, the reaction was stirred at room temperature for 16 h. The mixture was diluted with water and filtered through celite. The celite bed was washed with ethyl acetate. The combined filtrate and washings were extracted with ethyl acetate. The residue, obtained after evaporation, upon chromatography afforded a mixture of a single *trans* and single *cis* diastereomer. These two were easily separable by conventional chromatography over silica gel using hexane/ethyl acetate (4:1) as eluent.

carried out; the ^{1}H NMR spectra of the crude reaction mixtures 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 ^{1}H and ^{13}C NMR spectra with only one set of signals being present even in the presence of a chiral shift reagent [Eu(fod)$_3$]. As is evident from the data provided in Table 1, these reactions proceeded in good yields and exhibited excellent levels of stereochemical control. They have the added advantage of providing greater than 95% asymmetric induction in both the *cis* and *trans* product manifold. The reactions also worked with the same efficiency in the case of the easily removable[10a] oxazolidine **1b**, derived from *S*-phenylglycine. In the presence of a catalytic amount of CuI, the reaction was slow and required an excess of nitrone (>2 equiv.) to give similar yields and selectivity as observed using stoichiometric amounts of CuI. Nitrones derived from aliphatic aldehydes failed to provide decent yields of β-lactams.

The absolute stereochemistry of one of the compounds, **4c**, was determined by single crystal X-ray diffraction (Fig. 1). The absolute configuration (3*R*,4*S*) of the structure was determined, as indicated by the Flack parameter[14] of –0.07 and is in accordance with our prediction. Although it had been reported by Ding and Irwin that the *trans* compounds originated from the *cis* isomers by epimerization under basic conditions, we also demonstrated that this was indeed true. Thus, the *trans* isomer **4b** could be obtained from the *cis* isomer **3b** by treatment with *n*-BuLi at –20°C followed by quenching with NH_4Cl.

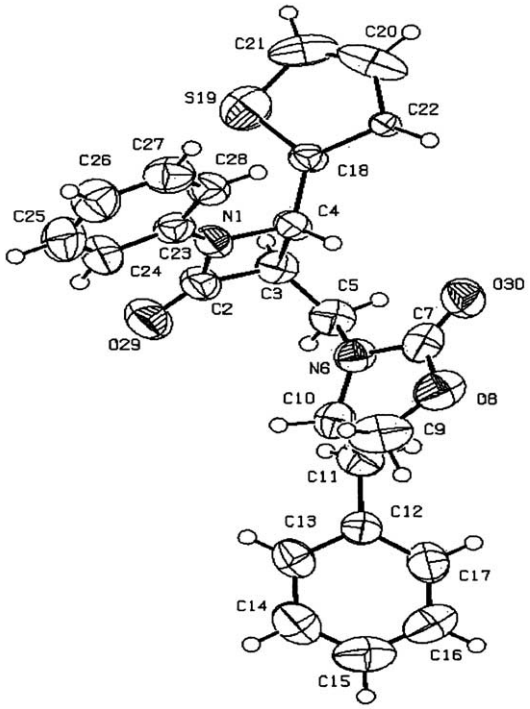


Figure 1. ORTEP diagram of **4c**.

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