Investigation on the copper (I) salts catalyzed asymmetric reaction of terminal alkynes with acyclic nitrones

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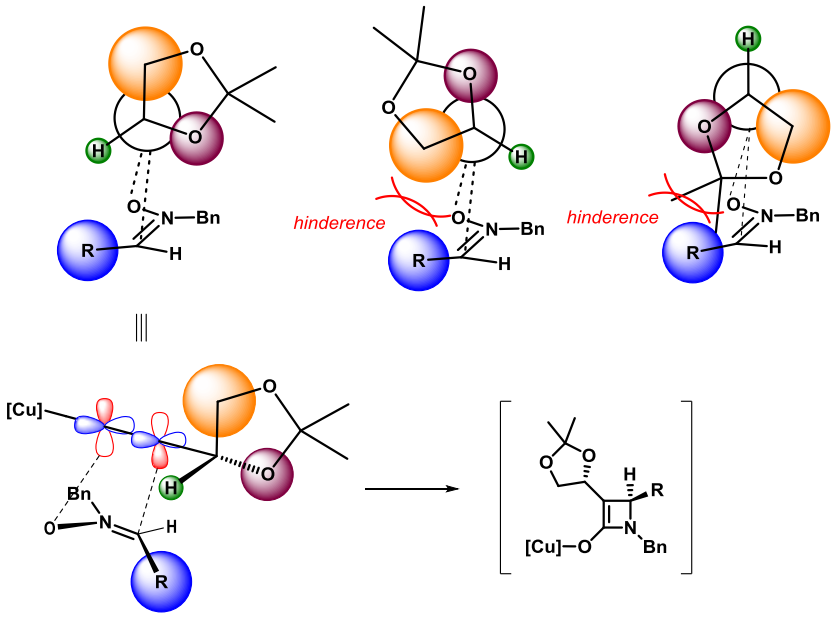
ABSTRACT

1. Diastereoselective synthesis of *β*-lactams via Kinugasa reaction of acyclic chiral nitrones.

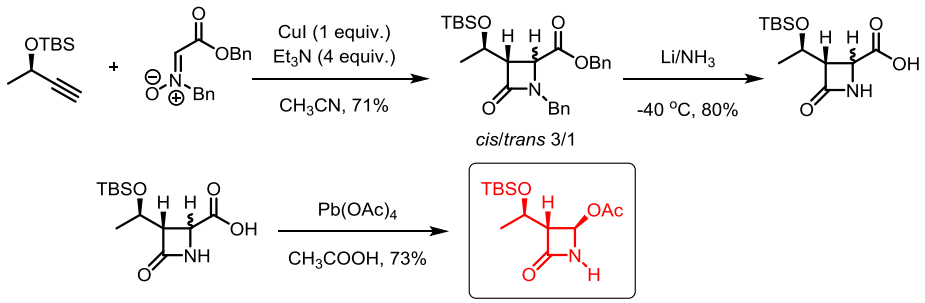
I demonstrated that simple acyclic chiral nitrones subjected to a copper(I)-catalyzed reaction with achiral alkynes provide the corresponding *β*-lactams with moderate asymmetric induction. This result is markedly different than the outcome observed for similar reactions involving chiral cyclic nitrones investigated by us earlier, which proceeded with high stereoselectivity. On the other hand, high steroselectivity of the Kinugasa cascade was observed for nonracemic alkynes. Due to the free rotation of the nitrone substituents, the direction and magnitude of the asymmetric induction at the C-4 carbon atom of the resulting azetidinone ring is governed by the stereochemistry of the acetylene. Owing to the linear symmetry of the triple bond, the nitrone approaches the acetylene molecule from between the small and the medium substituent of its stereogenic center with both syn substituents at the C=N double bond directed towards the hydrogen atom. This result stands in opposition to the conclusions drawn from our previous studies on cyclic nitrones. In a recent case when both a chiral acetylene and a chiral cyclic nitrone were used, the stereochemical outcome of the process depended only on the structure of the nitrone component of the reaction.



I showed also that electronic circular dichroism (ECD) in combination with NMR spectroscopy is a useful and effective method for reliable determination of the absolute configuration of all components of complex mixtures of azetidinones. High effectiveness of the chiral analysis of complex mixtures was demonstrated for HPLC coupled on-line with ECD detection as well.

2. A practical preparation of a key intermediate for penem and carbapenem synthesis.

I developed a new, practical and stereoselective synthesis of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone, a keyintermediate in the preparation of β-lactam antibiotics. The crucial step of the synthesis is based on the Cu(I)-mediated Kinugasa cycloaddition/rearrangement cascade between silyl-protected (*R*)-3-butyn-2-ol and a nitrone derived from benzylhydroxylamine and benzyl glyoxylate.



3. A simple and efficient one-pot synthesis of protected L-glyceraldehyde derivatives.

O,O-Ketals of L-glyceraldehyde, particularly the isopropylidene derivatives, represent valuable substrates in target-oriented synthesis. L-Glyceraldehyde can be obtained from L-mannitol following a two-step procedure involving the formation of a diacetal followed by a glycolic cleavage.Unfortunately, considering the high price of L-mannitol, such a method has only limited value. As a result of our research we developed a large-scale, simple, economic, and safe procedure for the preparation of L-glyceraldehyde acetonide under conditions, which allow its direct transformation (one-pot) into the desired products (acetylenes, nitrones). The title L-glyceraldehyde acetonide was obtained from readily available L-serine.