Copper-Bis(oxazoline) Catalyzed Synthesis of β-Lactams – Enantioselective Reaction of Alkynes with Nitrones

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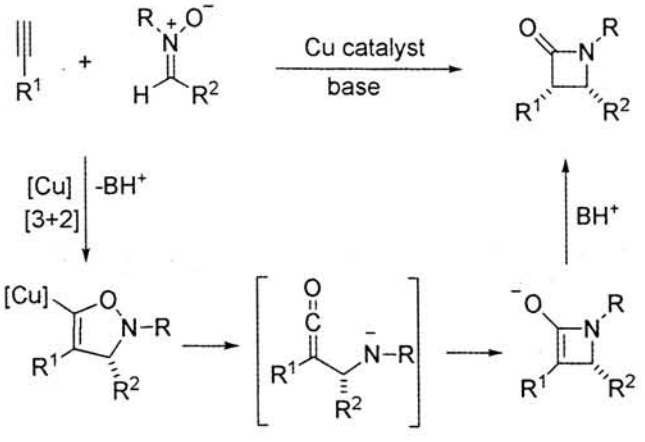
Background

β-Lactams are frequently found in natural and unnatural products with biological activity. They find application as antibiotics and protease inhibitors and are useful reagents in organic synthesis. Consequently, their stereoselective synthesis has attracted great interest. Most successful approaches in the enantioselective synthesis of β-lactams are dependent on chiral auxiliary based methods [1] whereas only a few catalytic enantioselective reactions have been reported. Among those the copper catalyzed reaction of alkynes with nitrones, the Kinugasa reaction, has provided a particularly attractive route to functionalized β-lactams (Scheme 1) [2]. In this transformation a copper acetylide is formed by the reaction of the Cu catalyst with the terminal alkyne followed by a [3+2] dipolar cycloaddition with the nitrone. The β-lactam is then obtained by ring opening fragmentation to the ketene, recyclization and protonation.



Scheme 1 Mechanism of the copper-catalyzed Kinugasa reaction.

Inspired by Kinugasa, the first asymmetric reaction using catalytic amounts of copper (I) iodide and bisoxazoline **A** (Figure 1) was reported by Miura and co-

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workers [3]. The β-lactam was obtained in moderate enantio- and diastereoselectivity in the single reaction of phenylacetylene with *N*-α-diphenylnitrone. Subsequently, Fu and coworkers have reported a catalytic enantioselective Kinugasa reaction using copper(I) chloride and a C_2-symmetric planar chiral bis(azaferrocene) ligand **B** (Figure 1)[4]. The reaction products were obtained in good to excellent enantio- and diastereoselectivities when conducted at low temperatures in the presence of Cy_2NMe. Most recently, chiral Cu(II)-tris(oxazoline) complexes **C** (Figure 1) were examined by Tang and coworkers in the enantioselective coupling of alkynes with nitrones, giving β-lactams in good enantio- and diastereoselectivities, but lower yields [5].

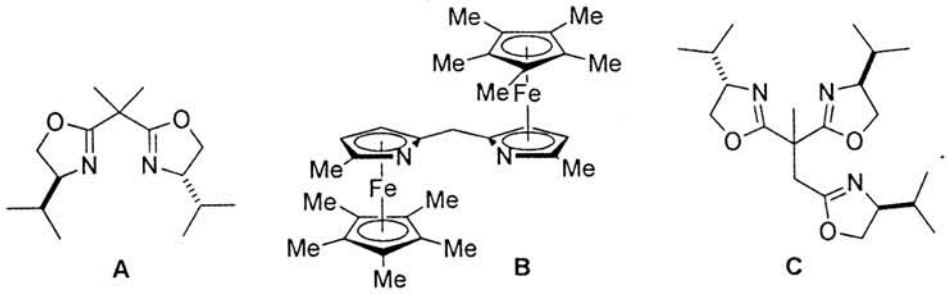
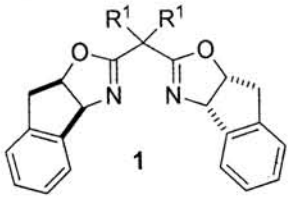


Figure 1 Chiral ligands used in the Kinugasa reaction.

Results

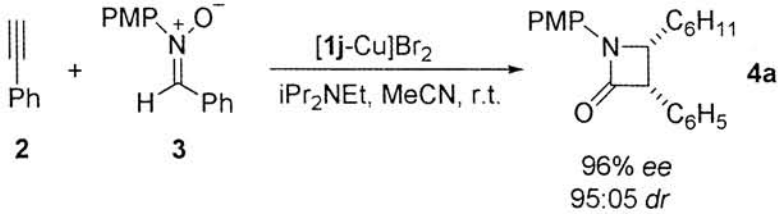
Recent reports from this laboratory and others have focused on the development of bis(oxazoline)-Cu(II) complexes as chiral Lewis acids for a variety of highly enantioselective transformations [6], such as Diels-Alder and hetero Diels-Alder reactions [7-8], cycloadditions [9], ene reactions [10], aldol reactions [11], Michael reactions [12], and amination reactions [13].

Intrigued by the Kinugasa reaction, this mild and practicable approach to the β-lactams, we speculated that sterically more demanding Cu-bisoxazoline catalysts could lead to better diastereo- and enantioselection. Therefore, we decided to test various box ligands in combination with copper salts in the Kinugasa reaction.



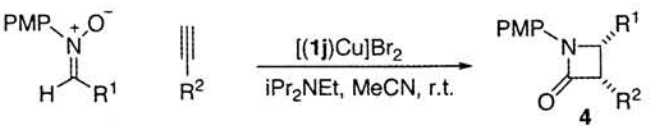
1a R^1 = Me
1b R^1 = Et
1c R^1 = H
1d R^1 = -$(CH_2)_2$-
1e R^1 = Bn
1f R^1 = -$CH_2C_6F_5$
1g R^1 = -CH_2(2,6-$Cl_2C_6H_3$)
1h R^1 = -CH_2(pyridyl)
1i R^1 = -CH_2(4-iPr-C_6H_4)
1j R^1 = -CH_2(4-tBu-C_6H_4)

From a survey of different ligands, as well as copper salts, solvents, and bases we found that the residues R^1 of the bis(oxazoline) skeleton **1** had the greatest impact on the reaction selectivities. While Cu catalysts prepared from the known indabox ligands **1a–1e** yielded only moderate enantioselectivities we decided to prepare the new ligands **1f–1j** and applied those in the Kinugasa reaction. From this comparison the [(**1j**)Cu]Br_2 complex proved to be the catalyst of choice providing the β-lactam **4a** in 96 % *ee* with 95:5 *cis:trans* diastereoselection (Scheme 2).



Scheme 2 Copper(II)-indabox catalyzed Kinugasa reaction.

Using the optimized conditions, we explored the scope of the [(**1j**)Cu]Br_2 catalyzed Kinugasa reaction. Table 1 shows examples of the copper bisoxazoline catalyzed reaction. All reactions were carried out using 10 mol% of catalyst in acetonitrile at ambient temperature. In general β-lactams generated from both aryl- and alkyl- substituted nitrones and alkynes exhibit high *cis*-diastereoselectivities and good to excellent enantiomeric excess.

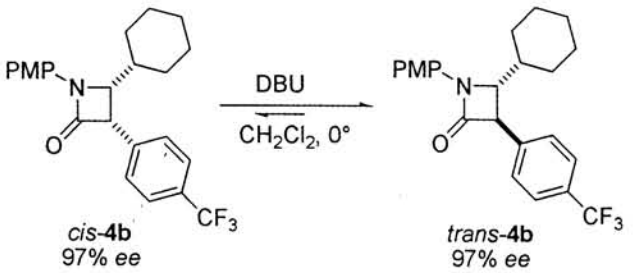


product	R^1	R^2	*cis/trans*	%yield (cis)	%*ee* (cis)
4a	C_6H_{11}	C_6H_5	95:05	64	96
4b	C_6H_{11}	4-$(CF_3)C_6H_4$	95:05	68	97
4c	C_6H_{11}	4-(OMe)C_6H_4	97:03	71	98
4d	C_6H_{11}	4-$(CH_3)C_6H_4$	91:09	70	98
4e	C_6H_{11}	1-cyclohexenyl	90:10	53	92
4f	$CH(CH_3)_2$	4-$(CF_3)C_6H_4$	94:06	60	98
4g	$CH(CH_3)_2$	4-(OMe)C_6H_4	90:10	69	98
4h	$CH(CH_3)_2$	4-$(CH_3)C_6H_4$	90:10	72	97
4i	$CH(CH_3)_2$	1-cyclohexenyl	90:10	41	91
4j	4-$(CO_2Me)C_6H_4$	C_6H_5	97:03	68	90
4k	4-$(CO_2Me)C_6H_4$	4-(OMe)C_6H_4	96:04	62	90
4l	4-$(CO_2Me)C_6H_4$	4-$(CH_3)C_6H_4$	97:03	65	88
4n	4-(OMe)C_6H_4	C_6H_5	98:02	68	86
4o	4-(OMe)C_6H_4	4-(OMe)C_6H_4	93:07	43	87
4p	4-(Br)C_6H_4	C_6H_5	95:05	72	86
4q	4-(Br)C_6H_4	4-(OMe)C_6H_4	94:06	69	89

Table 1 Examples of the copper bisoxazoline-catalyzed reactions performed at room temperature with 10 mol% catalyst loading for two days.

Additionally, one of the obtained β-lactams, *cis*-(3*S*,4*R*)-**4b** was epimerized to *trans*-**4b** by treatment with DBU in CH_2Cl_2, establishing that the copper bisoxazoline catalyzed process effectively provides stereoselective access to all possible isomers.

The absolute configuration of the obtained β-lactams can be explained by a proposed model based on the X-ray crystal structure of complex [(**1j**)Cu]Br_2 (Figure 2).



The observed stereochemistry of the β-lactam may be rationalized by assuming that in the transition state the alkyne and nitrone are bound to the copper catalyst and that the nitrone is approached from the *Si* face (Figure 2, right).

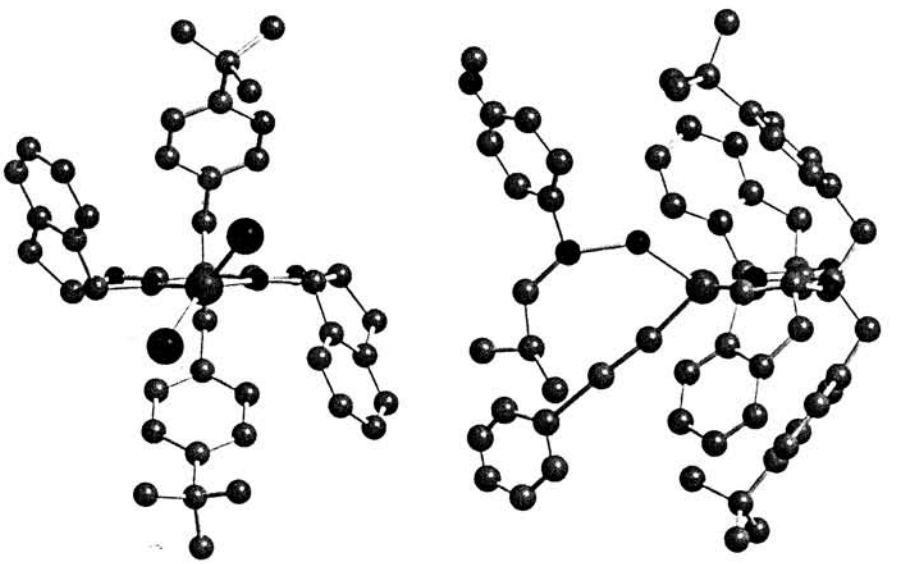


Figure 2 X-ray crystal structure of catalyst [(**1j**)Cu]Br_2 (left) and proposed model of a transition structure (right).

Summary

In summary, we have developed a highly diastereo- and enantioselective reaction of alkynes with nitrones, catalyzed by chiral copper-bis(oxazoline) complexes. This process provides a general and practical route to versatile β-lactams. The mild reaction conditions, functional group tolerance, and availability of alkynes and nitrones render it an attractive approach to various β-lactams. In addition to the reports of numerous other transformations, this study demonstrates once again that the structural flexibility of the readily accessible bisoxazoline ligands provides highly efficient Cu-catalysts that in many reactions are superior in performance to other catalyst systems.

CV of David A. Evans

David A. Evans was born in Washington D.C. in 1941. He received his A.B. degree from Oberlin College in 1963. He obtained his Ph.D. at the California Institute of Technology in 1967, where he worked under the direction of Professor Robert E. Ireland. In that year he joined the faculty at the University of California, Los Angeles. In 1973 he was promoted to the rank of Full Professor and shortly thereafter returned to Caltech where he remained until 1983. He then joined the Faculty at Harvard University and in 1990 he was appointed as the Abbott and James Lawrence Professor of Chemistry.

CV of Magnus Rüping

Magnus Rüping was born in Telgte, Germany, in 1972. He studied at the Technical University of Berlin, Trinity College Dublin and ETH Zürich. He obtained his Ph.D. in 2002 from ETH under the guidance of Professor Dieter Seebach. After carrying out postdoctoral work with Professor David A. Evans at Harvard University, he joined the Johann Wolfgang Goethe-University Frankfurt as Degussa Endowed Professor of Chemistry in fall 2004.

CV of Florian Kleinbeck

Florian Kleinbeck was born in Stuttgart, Germany, in 1978. He studied at the Technical University of München and ETH Zürich and completed his diploma thesis with Professor David A. Evans. In 2004 he joined Professor Erick M. Carreiras group for his Ph. D. studies.

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