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COMMUNICATIONS

Published on Web 04/05/2002

Cu(I)/Bis(azaferrocene)-Catalyzed Enantioselective Synthesis of β-Lactams via Couplings of Alkynes with Nitrones

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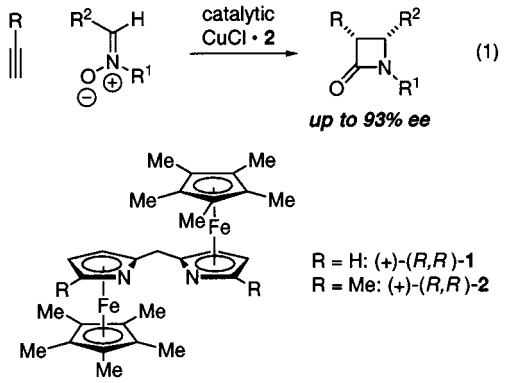
Received February 6, 2002

β-Lactams are an intensively studied family of heterocycles, due primarily to their biological activity.[1] Historically, they are best known for their use as powerful antibiotics (e.g., penicillins and cephalosporins), but more recently they have received attention for other therapeutic attributes, such as their capacity to lower cholesterol levels.[2] In addition to their importance as bioactive compounds, β-lactams serve as useful building blocks in synthetic organic chemistry (e.g., the commercial semisynthesis of the anticancer agent paclitaxel (Taxol) employs a β-lactam for the installation of the β-amino acid-derived side chain[3]).[1]

As a consequence of their wide-ranging significance, a great deal of effort has been dedicated to the development of methods for the stereoselective synthesis of β-lactams.[1] Although considerable progress has been achieved, nearly all of the approaches that have been described are based on the use of chiral, nonracemic precursors;[1] direct catalytic enantioselective routes to β-lactams are rare. In fact, to the best of our knowledge, only five such methods have been reported: the rhodium-catalyzed carbonylation of an aziridine (kinetic resolution),[4] the rhodium-catalyzed intramolecular insertion of an α-diazo amide into a C−H bond,[5] the copper-catalyzed coupling of an alkyne with a nitrone (see below),[6] the aminoether-catalyzed reaction of ester enolates with imines,[7] and the alkaloid-catalyzed ketene−imine cycloaddition.[8] While each of these discoveries represents an important advance toward the objective of a general method for the catalytic enantioselective synthesis of β-lactams, each suffers from significant limitations in scope or stereoselection.[9]

We were intrigued by a report of Kinugasa in 1972 that describes a convergent route to β-lactams through the reaction of a copper acetylide with a nitrone.[10,11] Appealing features of this process include the ready availability of the starting materials (terminal alkynes and nitrones) and its high functional-group tolerance (e.g., alcohols, halides, amines, and esters). Miura subsequently determined that the Kinugasa reaction can be accomplished with a catalytic amount of copper in conjunction with a terminal alkyne, and he provided the only description of asymmetric catalysis of this powerful transformation.[6] Miura examined one substrate pair (phenylacetylene and *N*,α-diphenylnitrone) and obtained a maximum ee of 57% (10% CuI, 20% bisoxazoline ligand; 50% yield; probably ∼2:1 cis:trans). In this communication, we establish that, using a new C_2-symmetric planar-chiral bis(azaferrocene) ligand (**2**), we can achieve catalytic enantioselective Kinugasa reactions that generate β-lactams with good enantiomeric excess and cis diastereoselection (eq 1).

We have reported that bis(azaferrocene) ligand **1** furnishes useful stereoselectivity in copper-catalyzed cyclopropanations of olefins[12] and ring expansions of oxetanes.[13] In our initial studies of the Kinugasa reaction, we examined the utility of **1** in the coupling of phenylacetylene with *N*,α-diphenylnitrone under Miura's conditions;



disappointingly, we observed moderate stereoselection. Fortunately, however, our ligand design allows us to readily modify the chiral environment of the bis(azaferrocene). Accordingly, we synthesized new, methyl-substituted ligand **2** (from commercially available compounds in three steps and a resolution), optimized the reaction conditions, and obtained good stereoselectivity (Table 1, entry 1).[14]

We have investigated the impact on stereoselection of the electronic character of the N-bound aromatic group of the nitrone (Table 1).[15] Generation of the β-lactam proceeds with excellent cis diastereoselectivity irrespective of the nature of the aromatic ring (∼95:5; entries 1−5). With regard to enantioselectivity, the more electron-rich the aromatic group, the higher the ee; there is, however, a tradeoff between ee and yield (entries 1−4). The very good diastereo- and enantioselection that we obtain with the 4-anisyl substituent (entry 2) is particularly noteworthy, since this is a common N-protecting group for β-lactams.[16] A comparison of entries 4 and 5 reveals that we can enhance the stereoselectivity and the yield by lowering the reaction temperature.

Focusing on 4-anisyl-protected substrates, we turned our attention to determining the scope with respect to the nitrone component (Table 2). We established that CuCl/**2** is effective for the catalytic enantioselective formation of β-lactams from a variety of nitrones, with substituents on carbon ranging from aromatic (entries 1−3) to alkyl (entry 4) to acyl (entry 5).

We have also investigated the scope of this process with respect to the alkyne component, focusing on couplings with alkyl- and acyl-substituted nitrones (**3** and **4**, respectively, in Table 3). Both families react with aromatic alkynes to generate β-lactams with excellent diastereo- and enantioselectivity (entries 1−3 and 5). Although alkyl-substituted acetylenes are converted to the desired product with somewhat lower stereoselection (entry 4), alkenyl-substituted substrates furnish good de and ee (entry 6). It is worth noting that, since Brønsted base-catalyzed cis → trans isomerization of β-lactams is well-established,[17] our enantioselective Cu/**2**-catalyzed process effectively provides stereoselective access to all four of the possible isomers.

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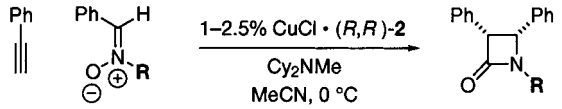
10.1021/ja025833z CCC: $22.00

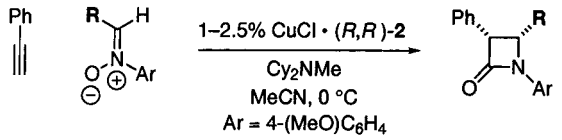
Table 1. Catalytic Asymmetric Synthesis of β-Lactams: Variation of the N-Substituent[a]



entry	R	cis:trans	% ee, cis	isolated yield cis isomer (%)
1	Ph	95:5	77	69
2	4-(MeO)C_6H_4	95:5	85	53
3	4-BrC_6H_4	94:6	72	74
4	4-(EtO_2C)C_6H_4	94:6	67	79
5[b]	4-(EtO_2C)C_6H_4	95:5	71	91

[a] All data represent the average of two runs. [b] Run at −20 °C.

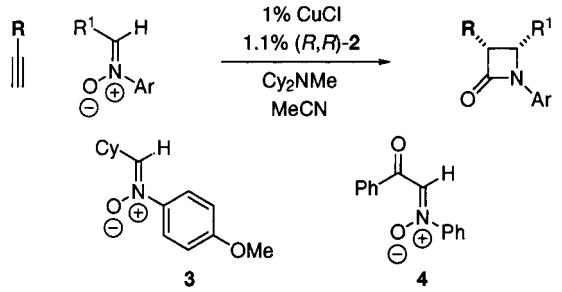
Table 2. Catalytic Asymmetric Synthesis of β-Lactams: Scope with Respect to the Nitrone Component[a]



entry	R	cis:trans	% ee, cis	isolated yield cis isomer (%)
1	Ph	95:5	85	53
2	4-(F_3C)C_6H_4	93:7	90	50
3[b]	4-(MeO)C_6H_4	93:7	83	46
4	Cy	93:7	89	57
5	PhCO	91:9	72	42

[a] All data represent the average of two runs. [b] Run at rt.

Table 3. Catalytic Asymmetric Synthesis of β-Lactams: Scope with Respect to the Alkyne Component[a]



entry	nitrone	R	cis:trans	% ee, cis	isolated yield cis isomer (%)
1[b]	3	Ph	>95:5	92	65
2[b]	3	4-(F_3C)C_6H_4	>95:5	93	57
3[b]	3	4-(MeO)C_6H_4	92:8	91	60
4[b]	3	$PhCH_2$	71:29	73(70)	43(17)
5[c]	4	Ph	90:10	90	56
6[c]	4	1-cyclohexenyl	90:10	91	45

[a] All data represent the average of two runs. The values in parentheses provide data for the trans isomer. [b] Run at −20 °C. [c] Run at −40 °C.

In conclusion, we have developed the first versatile system for the copper-catalyzed asymmetric coupling of alkynes with nitrones to form β-lactams. In terms of scope and stereoselection, this method compares favorably with previously reported strategies for the catalytic enantioselective synthesis of this important family of heterocycles. Other appealing attributes of this process include the ready availability of the starting materials, the functional-group tolerance of the reaction, and the convergency of the approach.

Note Added in Proof: We have recently communicated that, using a planar-chiral heterocycle as the catalyst, β-lactams can be prepared from symmetrical or unsymmetrical disubstituted ketenes and a variety of imines with enantiomeric excesses up to 98%.[18]

Acknowledgment. Support has been provided by Bristol-Myers Squibb, Novartis, and Pfizer. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by NSF CHE-9808061 and NSF DBI-9729592.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: New York, 1992. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Volumes 1−3. (c) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993. (d) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 1B, Chapters 1.18−1.20. (e) *Synthesis of β-Lactam Antibiotics*; Bruggink, A., Ed.; Kluwer: Dordrecht, Netherlands, 2001. (f) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377−386. Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389. (g) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

(2) For a discussion, see: Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973−980. See also: http://www.sch-plough.com/news/2002/research/20020318.html(accessed March 2002).

(3) For leading references, see: Kingston, D. G. I. *Chem. Commun.* **2001**, 867−880.

(4) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931−934.

(5) (a) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983−5986. (b) Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992**, *33*, 7819−7822. Doyle, M. P.; Kalinin, A. V. *Synlett* **1995**, 1075−1076. (c) Watanabe, N.; Anada, M.; Hashimoto, S.-i.; Ikegami, S. *Synlett* **1994**, 1031−1033. Hashimoto, S.-i.; Watanabe, N.; Anada, M.; Ikegami, S. *J. Synth. Org. Chem., Jpn.* **1996**, *54*, 988−999. Anada, M.; Watanabe, N.; Hashimoto, S.-i. *Chem. Commun.* **1998**, 1517−1518. Anada, M.; Hashimoto, S.-i. *Tetrahedron Lett.* **1998**, *39*, 9063−9066.

(6) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999−5004.

(7) (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060−2061. (b) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715−716.

(8) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(9) (a) Rhodium-catalyzed carbonylation of an aziridine (kinetic resolution): scope = two examples, both 1-*tert*-alkyl-2-phenyl aziridines; ≥1 equiv of ligand was used. (b) Rhodium-catalyzed intramolecular insertion of an α-diazo amide into a C−H bond: scope = effective for the synthesis of certain bicyclic systems and of 4-substituted-1-*tert*-butyl-3-methoxycarbonyl-2-azetidinones. (c) Copper-catalyzed coupling of an alkyne with a nitrone: scope = one example; ee: 57%; cis:trans ~2:1; yield: 50%. (d) Aminoether-catalyzed reaction of ester enolates with imines: scope = one enolate. (e) Alkaloid-catalyzed ketene−imine cycloaddition: scope = one imine; yields: 36−65%.

(10) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466−467.

(11) For examples of applications of the Kinugasa reaction by others, see: (a) Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2382−2386. (b) Dutta, D. K.; Boruah, R. C.; Sandhu, J. S. *Indian J. Chem.* **1986**, *25B*, 350−353. Dutta, D. K.; Boruah, R. C.; Sandhu, J. S. *Heterocycles* **1986**, *24*, 655−658. (c) Basak, A.; Bhattacharya, G.; Bdour, H. M. M. *Tetrahedron* **1998**, *54*, 6529−6538.

(12) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270−10271.

(13) Lo, M. M.-C.; Fu, G. C. *Tetrahedron* **2001**, *57*, 2621−2634.

(14) The use of a sterically demanding trialkylamine (1.0 equiv or less) as the base is essential to obtain good cis diastereoselectivity in the reaction.

(15) The reaction proceeds much more slowly when the substituent on nitrogen is an alkyl group.

(16) (a) Wild, H. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; Chapter 1. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 636−637.

(17) For examples, see: (a) Reference 6. (b) Fujisawa, T.; Ichikawa, M.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307−1310. (c) Shimizu, M.; Kume, K.; Fujisawa, T. *Chem. Lett.* **1996**, 545−546.

(18) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578−1579.

JA025833Z