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A Highly Stereoselective Synthesis of Chiral α-Amino-β-lactams via the Kinugasa Reaction Employing Ynamides†

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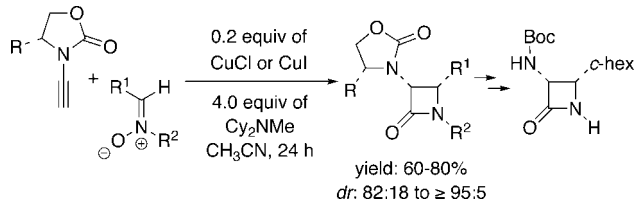
ABSTRACT



A highly stereoselective synthesis of chiral α-amino-β-lactam through an ynamide-Kinugasa reaction is described. In addition, a mechanistic model is illustrated here to rationalize the observed diastereoselectivity, which depends on both the initial [3 + 2] cycloaddition step and the subsequent protonation for which both are highly selective.

Since Staudinger's first preparation,[1] β-lactams have captured the attention of synthetic and medicinal communities for nearly a century.[2–6] Rendered famous by penicillin, those substituted with α-amino groups are among the most sought after β-lactams. Consequently, an impressive array of stereoselective approaches toward chiral α-amino-β-lactams has been reported.[4–6] While the Kinugasa reaction[7,8] represents an elegant approach toward β-lactams, it has remained relatively unexplored until recently, and this is particularly true in the development of enantioselective protocols.[9–11] With such immense significance, we recognized the unique potential of an ynamide-Kinugasa reaction. As shown in Scheme 1, reactions of chiral ynamides **1**[12,13] with nitrones in a Kinugasa manner would not only lead to a stereoselective manifold for constructing β-lactams, but also more impor-

† This paper is dedicated in memory of Dr. Christopher R. Schmid (1959–2007) of Eli Lilly.

(1) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51.

(2) (a) Page, M. I. *The Chemistry of β-Lactams*;, Blackie Academic and Professional: New York, 1992. (b) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993.

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(4) For reviews on synthetic approaches, see:(a) Miller, M. J. *Acc. Chem. Soc.* **1986**, *19*, 49. (b) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. (c) Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Syntheses*; Trost, B.,; Flemming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, p 85. (d) Van der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503. (e) Hegedus, L. S. *Acc. Chem. Soc.* **1995**, *28*, 299. (f) Ojima, I. *Acc. Chem. Soc.* **1995**, *28*, 383. (g) Ojima, I.; Delaloge, F. *Chem. Soc. Rev* **1997**, *26*, 377. (h) DeKimpe, N. In *Comprehensive Heterocyclic Chemistry II* ; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Padwa, A.,. Eds.; Pergamon: Oxford, UK, 1996; Vol. 1B. (i) Palomo, C.; Aizpurua, J. M.; Inaki, G.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (j) *Synthesis of β-Lactams Antibiotics. Chemistry, Biocatalysis and Process Integration;* Bruggink, A., Ed.; Kluwer: Dordrecht, The Netherlands, 2001. (k) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10. (l) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*592.

(5) For Rh-catalyzed asymmetric manifolds, see:(a) Doyle, M. P.; Pieters, R. J.; Tauton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820. (b) Anada, M.; Watanabe, N.; Hashimoto, S. *Chem. Commun.* **1998**, 1517. (c) Davioli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518.

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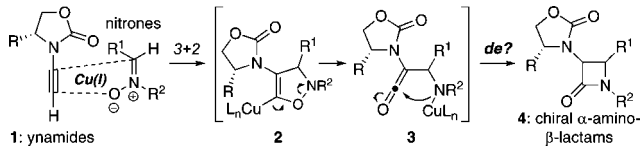
Scheme 1. An Ynamide-Kinugasa Reaction

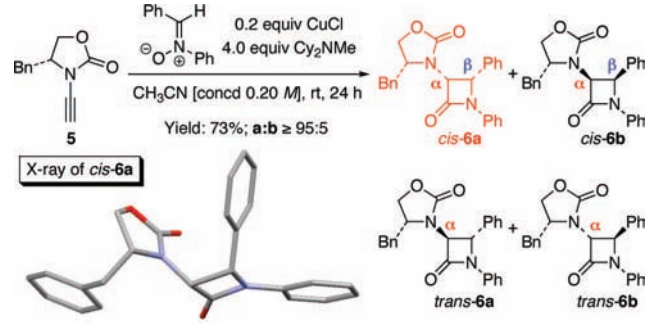


tantly provide a direct synthesis of chiral α-amino-β-lactams (see **4**). We report here a highly stereoselective ynamide-Kinugasa reaction.

The feasibility of an ynamide-Kinugasa reaction was readily established by employing ynamide **5** (Scheme 2). With 0.2 equiv of CuCl and 4.0 equiv of Cy_2NMe, the reaction of **5** with *N*-benzylidene-*N*-phenylnitrone proceeded effectively in CH_3CN at rt to give β-lactam *cis*-**6a**[14] in 73% yield as the major isomer. X-ray structural analysis unambiguously revealed that the relative stereochemistry between the α- and β-carbons is *cis*. This suggests that the minor isomer(s) could be *cis*-**6b** and/or *trans*-**6a/6b** with **a**/**b** isomers differing at the β-carbon stereochemistry.

The scope of this reaction is distinctly diverse. As shown in Table 1, we found several interesting features: (1) Sterically more encumbered auxiliaries retard the reaction

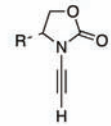
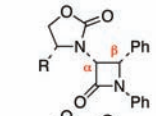
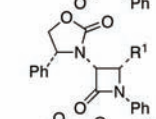
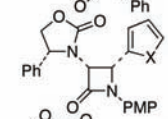
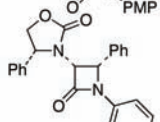
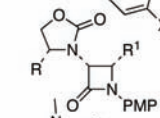
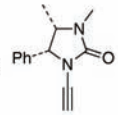
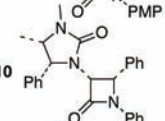
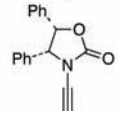
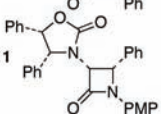
Scheme 2. Establishing the Feasibility and Stereochemistry



rate (entries 2 and 3 versus 1); (2) CuI is also feasible as a catalyst and can be more effective than CuCl (entries 3, 6, 8, 13, and 15); and (3) the minor isomer **b** was assigned as *trans* initially based on proton coupling constants[15] (entries 5−7, 11, and 13) and was confirmed later via NOE experiments (vide infra).

An immediate application of this reaction is the preparation of chiral α-amino-β-lactams (Scheme 3). Toward this goal,

Table 1. Scope of the Ynamide-Kinugasa Reaction

entry	ynamides		α-amino-β-lactams	yield [%][a]	*dr*: [a:b][b]
1		7	 **12:** R = Ph	80	≥ 95:5
2		8	**13:** R = *i*-Pr	36	≥ 95:5
3		9	**14:** R = $CHPh_2$	28[c,d]	nd[e]
4		7	 **15:** R^1 = 4-Br-Ph	77	≥ 95:5
5		7	**16:** R^1 = [1]Naph	71	90:10
6		7	**17:** R^1 = styryl	72[c,f]	93:7
7		7	 **18:** X = O	61[c]	82:18
8		7	**19:** X = S	60[c,g]	≥ 95:5
9		7	 **20:** X = Cl	65	≥ 95:5
10		7	**21:** X = CO_2Et	63	≥ 95:5
11		5	 **22:** R = Bn; R^1 = Ph	59[h]	91:9
12		7	**23:** R = Ph; R^1 = Ph	60[h]	≥ 95:5
13		7	**24:** R = Ph; R^1 = *c*-hex	60[c,i,h]	92:8
14		10	 **25**	61	≥ 95:5
15		11	 **26**	60[c,h]	≥ 95:5

[a] Reaction conditions are as shown in Scheme 2 unless otherwise indicated. All are isolated yields. [b] dr is determined by using ^{1}H NMR. All isomers **a** are *cis*. The minor isomer **b** is *trans*. [c] 0.2 equiv of CuI was used, and the reaction was run at 0 °C to rt. [d] With 0.2 equiv of CuCl, the yield was 13%. [e] nd: not determined. [f] With 0.2 equiv of CuCl, yield was 71% and dr = 91:9. [g] With 0.2 equiv of CuCl, yield was 48% and dr = 86:14. [h] PMP: *p*-methoxyphenyl. [i] With 0.2 equiv of CuCl and 4.8 equiv of Hünig's base, yield was 54% and dr = 87:13.

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

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(10) For an earliest account, see:Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

(11) For stereoselective approaches, see:(a) Pal, R.; Basak, A. *Synlett* **2007**, 1585. (b) Pal, R.; Basak, A. *Chem. Commun.* **2006**, 2992. (c) Basak, A.; Ghosh, S. C.; Bhowmick, T.; Das, A. K.; Bertolasi, V. *Tetrahedron Lett.* **2002**, *43*, 5499. (d) Basak, A.; Mahato, T.; Bhattacharya, G.; Mukherjee, B. *Tetrahedron Lett.* **1997**, *38*, 643.

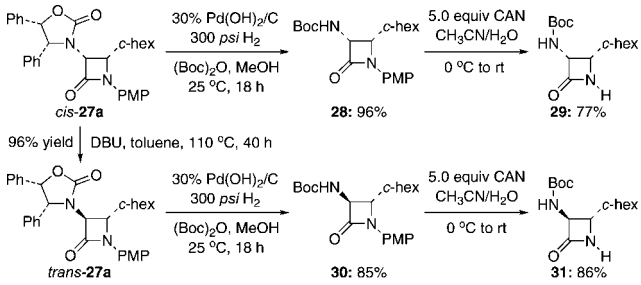
(12) For reviews on ynamides, see:(a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.

(13) For recent references on the chemistry of ynamides, see:(a) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. (b) You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, 1656. (c) Hashimi, A. S. K.; Salathe, R.; Frey, W. *Synlett* **2007**, 1763. (d) For a special issue dedicated to the chemistry of ynamides, see: Tetrahedron-Symposium-In-Print: Chemistry of Electron-Deficient Ynamines and Ynamides. *Tetrahedron* **2006**, *62*, Issue No. 16.

(14) See the Supporting Information.

(15) The range of proton couple constants for our *cis*-β-lactams is 5.0−5.6 Hz, and it is 2.0−2.4 Hz for *trans*-β-lactams.

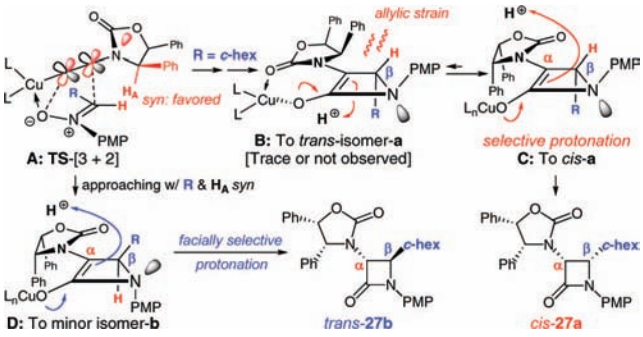
Scheme 3. Synthesis of Chiral α-Amino-β-lactams



we prepared *cis*-**27a** in 44−62% yield from **11** with an **a**:**b** ratio of in the range of 10:1−19:1. Hydrogenation with Boc-protection followed by oxidative removal of the PMP group in *cis*-**27a** with use of CAN provided chiral α-amino-β-lactam **29**. An α-epimerization of *cis*-**27a** via refluxing in toluene in the presence of DBU for 40 h afforded *trans*-**27a**, which could be converted to the isomeric α-amino-β-lactam **31** through the same sequence used for *cis*-**27a**.

During the isolation of *cis*-**27a**, we were able to attain a clean sample of the minor isomer *trans*-**27b** and confirmed its relative stereochemistry between the α- and β-carbons using NOE experiments.[14] We also isolated a small sample of *cis*-**27b** and spectroscopically observed a trace amount of *trans*-**27a**. Neither had been seen in other reactions. The assignment of *cis*-**27b** was confirmed through α-epimerization to *trans*-**27b** with DBU.[14] With these assignments, this ynamide-Kinugasa reaction became very intriguing from a stereochemical perspective. A unified mechanistic model is proposed in Scheme 4.

Scheme 4. A Proposed Mechanistic Model



On the basis of the assumption that the more reactive of the two π-bonds is the one conjugated with the nitrogen lone pair (all in red), the Cu(I)-promoted nitrone-[3 + 2] cycloaddition via intermediate **A** could diverge into two pathways that would determine the β-carbon stereochemistry. The preferred pathway would involve the approaching nitrone with its vinyl hydrogen (in red) being *syn* to H_A on the chiral auxiliary and the larger R group (*c*-hex in blue) *anti* to H_A to minimize steric interactions. This pathway would lead to intermediate **B** (skipping respective intermediates **2** and **3** shown in Scheme 1), and while **B** could undergo protonation at the more open bottom face away from the phenyl rings, it would lead to the *trans*-isomer **a** that was not observed from most of these reactions. Therefore, we reason that a facially selective protonation takes place instead via intermediate **C** on the top face to give *cis*-**27a** because **C** is more stable than **B** given the presence of allylic strain.

On the other hand, the less favorable cycloaddition pathway would involve the larger R group approaching *syn* relative to H_A on the auxiliary, and should lead to minor isomers **b** via related intermediate **D**. We believe a facially selective protonation also occurs here in **D** to provide *trans*-**27b** as the most dominant minor isomer. Intriguingly, B3LYP-6-31G* calculations reveal that *trans*-**27a** is ∼2.50 kcal mol^{-1} more stable than *cis*-**27a**, and *trans*-**27b** is ∼4.86 kcal mol^{-1} more stable than *cis*-**27b**. This implies that for the major reaction pathway, a facially selective protonation gives the kinetic product *cis*-**27a**, whereas a selective protonation in the minor reaction pathway gave the more stable *trans*-**27b**. Resubjecting *cis*-**27b** to the same reaction conditions did not lead to any α-epimerization or observation of *trans*-**27b.** Therefore, despite being more stable, *trans* isomers are not likely derived from α-epimerizations of their respective *cis* isomers.

We have described here a highly stereoselective ynamide-Kinugasa reaction and featured its application as a stereoselective manifold for constructing chiral α-amino-β-lactam. A proposed model reveals that the observed selectivity requires both the initial cycloaddition and subsequent protonation to be stereoselective.

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Supporting Information Available: Experimental procedures as well as ^1H NMR spectra and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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