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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-l actams 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-lact ams. 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-Kinugas a 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-l actams, but also more importantly, provide a direct synthesis of chiral α-amino-β-lactams [see **4**]. We report here a highly stereoselective ynamide-Kinugas a reaction.

The feasibility of an ynamide-Kinugasa reaction was readily established employing ynamide **5** [Scheme 2]. With 0.2 equiv CuCl and 4.0 equiv Cy_2NMe, the reaction of **5** with *N*-benzylidene-*N*-phenyl nitrone 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 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, and 13]; 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].

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Supporting Information Available: Experimental procedures as well as ^1H NMR spectral and characterizations are available for all new compounds and free of charge via Internet http://pubs.acs.org.

An immediate application of this reaction is the preparation of chiral α-amino-β-lactams [Scheme 3]. Toward this goal, 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** using 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** using 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.

Based on 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**. Re-subjecting *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-Kinugas a 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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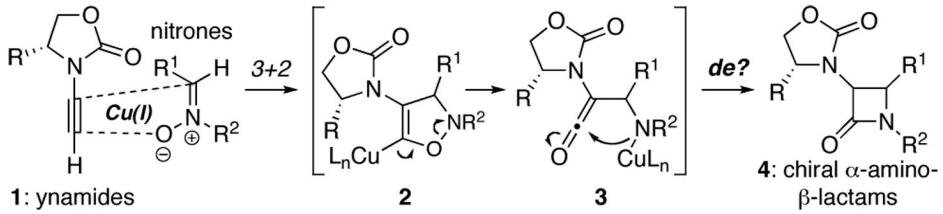
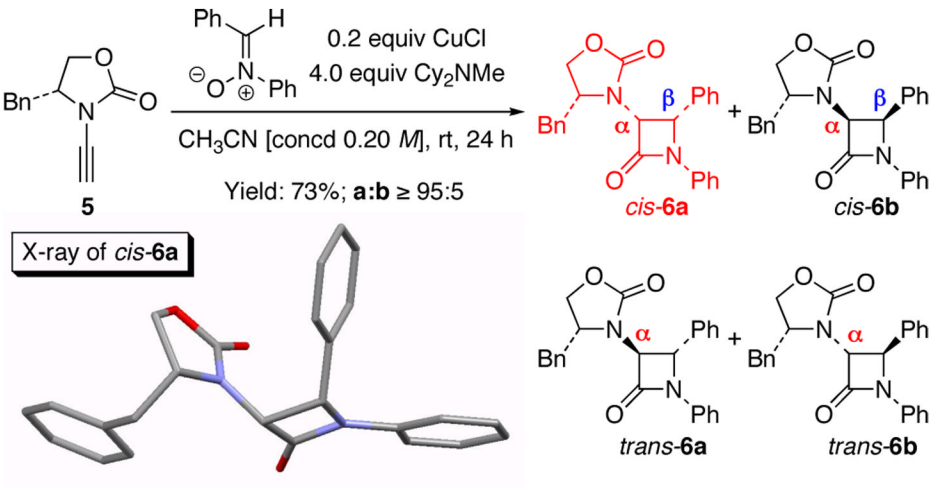
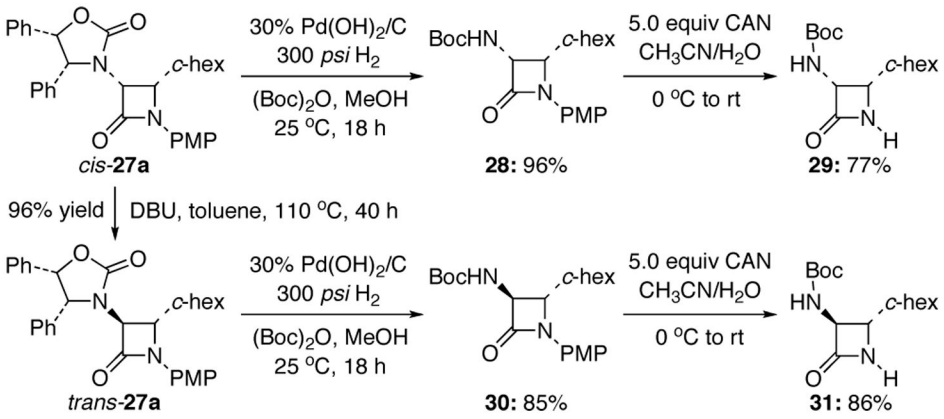
14. See Supporting Information
15. The range of proton couple constants for our *cis*-β-lactams is 5.0–5.6 Hz, and it is 2.0–2.4 Hz for *trans*-β-lactams



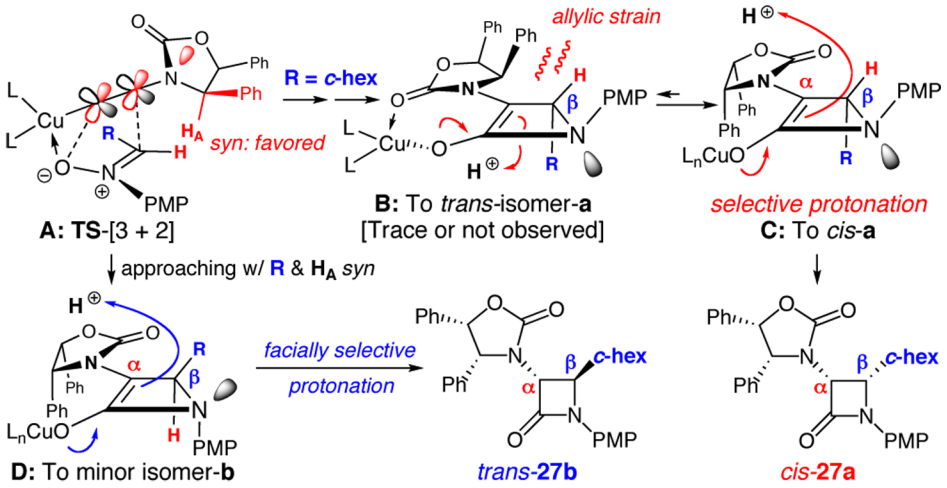
Scheme 1.
An Ynamide-Kinugasa Reaction



Scheme 2.
Establishing the Feasibility and Stereochemistry.



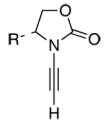
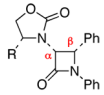
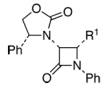
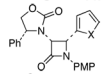
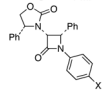
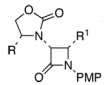
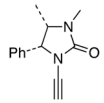
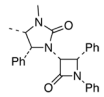
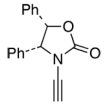
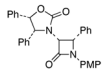
Scheme 3.
Synthesis of Chiral α-Amino-β-Lactams.



Scheme 4.
A Proposed Mechanistic Model.

Table 1

Scope of 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 = 1Naph	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 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: *para*-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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