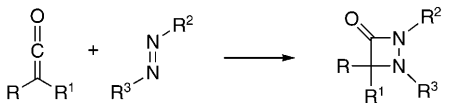
Asymmetric Catalysis

DOI: 10.1002/anie.200802439

# Enantioselective Nucleophilic Catalysis: The Synthesis of Aza-β-Lactams through [2 + 2] Cycloadditions of Ketenes with Azo Compounds**

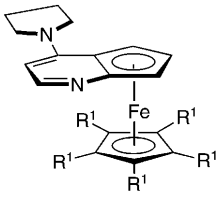
*Jacob M. Berlin and Gregory C. Fu**

Even though aza-β-lactams have attracted interest because of their biological activity[1] and their utility as intermediates in organic chemistry (e.g., for the generation of α-amino acids and hydantoins),[2–4] only limited progress has been reported with regard to the enantioselective synthesis of this family of heterocycles.[5] One attractive, convergent approach to the formation of aza-β-lactams is the [2 + 2] cycloaddition of a ketene with an azo compound [Eq. (1)].[6] To the best of our knowledge, no stereoselective variants of this process have yet been reported.



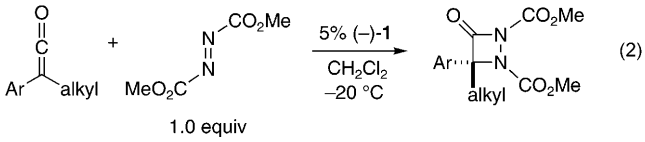
(1)

We have been exploring the use of chiral derivatives of PPY (4-pyrrolidinopyridine; e.g., **1** and **2**) as enantioselective catalysts for an array of transformations,[7] including couplings of ketenes with imines[8] or with aldehydes.[9,10] Although there are no reports of nucleophilic catalysis for [2 + 2] cycloadditions of ketenes with azo compounds, we were intrigued by the possibility that our planar-chiral pyridines might be effective in this role. Herein, we establish that PPY derivative **1** effects the first catalytic asymmetric synthesis of aza-β-lactams, through [2 + 2] cycloadditions of ketenes with azo compounds [Eq. (2)].



$R^1$ = Me: (–)-**1**
= Ph: (–)-**2**

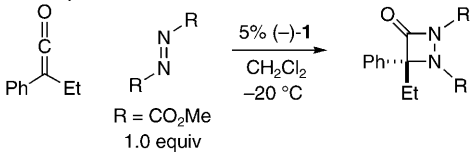
Initially, we examined the cycloaddition of phenyl ethyl ketene with dimethyl azodicarboxylate (1.0 equiv). We found that the planar-chiral PPY derivative **1** serves as an effective catalyst for the desired coupling, and generates the aza-β-lactam in good yield and enantioselectivity (Table 1, entry 1; in the absence of a catalyst there is no reaction: Table 1, entry 2).



1.0 equiv

(2)

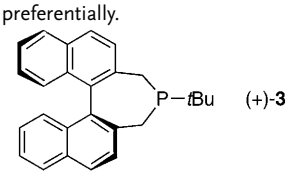
***Table 1:*** Effect of changing the "standard" reaction conditions (outlined in the equation below) in the nucleophile-catalyzed enantioselective synthesis of aza-β-lactams.



R = $CO_2$Me
1.0 equiv

| Entry | Change from the "standard" reaction conditions | *ee* [%] | Yield [%] |
|---|---|---|---|
| 1 | none | 86 | 89 |
| 2 | no (–)-**1** | – | < 5 |
| 3 | (–)-**2**, instead of (–)-**1** | –15[a] | 65 |
| 4 | (+)-**3**, instead of (–)-**1** | < 5 | 65 |
| 5 | quinine, instead of (–)-**1** | – | < 5 |
| 6 | R = $CO_2$Et | 80 | 85 |
| 7 | R = $CO_2$*i*Pr | 32 | 81 |
| 8 | R = $CO_2CH_2CCl_3$ | 20 | 20 |
| 9 | R = CO(piperidinyl) | – | < 5 |
| 10 | $ClCH_2CH_2Cl$, instead of $CH_2Cl_2$ | 87 | 65 |
| 11 | –30 °C | 85 | 68 |
| 12 | –10 °C | 73 | 68 |

[a] A negative *ee* value signifies that the opposite enantiomer of the product is formed preferentially.



(+)-**3**

Under the same reaction conditions, a related catalyst (**2**), as well as a variety of chiral phosphines and cinchona alkaloids, provide poor enantioselectivity or little of the cycloaddition product (Table 1, entries 3–5).[11,12] The substituents of the azo compound have a significant impact on the *ee* value and the yield, with the methoxycarbonyl group affording the best results (Table 1, compare entry 1 with entries 6–9). If

[*] Dr. J. M. Berlin, Prof. Dr. G. C. Fu
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-324-3611
E-mail: gcf@mit.edu

[**] We thank Dr. Xing Dai, Dr. Maximilian Dochnahl, and Takashi Nakai for helpful discussions and for experimental assistance. Support was provided by the NIH (National Institute of General Medical Sciences: grant no. R01-GM57034), Merck Research Laboratories, and Novartis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802439.

$ClCH_2CH_2Cl$ rather than $CH_2Cl_2$ is employed as the solvent, then the formation of the aza-β-lactam is less efficient (Table 1, compare entry 1 with entry 10). The reaction temperature of choice appears to be −20 °C (Table 1, compare entry 1 with entries 11 and 12).[13]

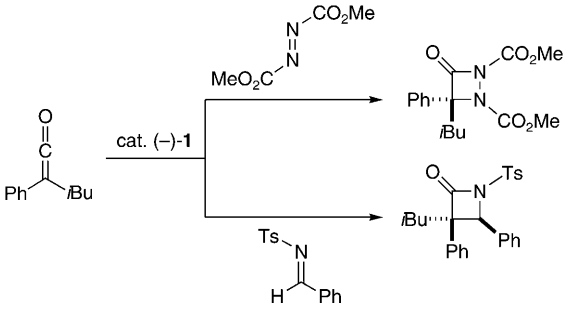
The optimized reaction conditions can be applied to the enantioselective synthesis of aza-β-lactams when starting from a variety of ketenes (Table 2). If the alkyl group is small (i.e., Me or a primary substituent), then the desired heterocycle is generally produced with good (but not excellent) enantioselectivity (≈85 % *ee*; Table 2, entries 1–7). Fortunately, the *ee* values of the aza-β-lactam products is readily enhanced by recrystallization (e.g., the product generated from phenyl ethyl ketene can be obtained in > 99 % *ee* after a single recrystallization; see Table 2, entry 2). In the case of ketenes that bear a secondary alkyl group, catalyst **1** typically furnishes the aza-β-lactam with very good enantioselectivity and yield (> 90 % *ee*; Table 2, entries 8–13).[14]

***Table 2:*** Nucleophile-catalyzed enantioselective synthesis of aza-β-lactams (see [Eq. (2)] for the reaction conditions).[a]

| Entry | Ar | Alkyl | *ee* [%] | Yield [%][b] |
|---|---|---|---|---|
| 1 | Ph | Me | 85 | 53 |
| 2 | Ph | Et | 86 (> 99)[c] | 89 |
| 3 | *m*-tolyl | Et | 85 | 79 |
| 4 | *o*-tolyl | Et | 67 | 46 |
| 5 | *o*-anisyl | Et | 93 | 89 |
| 6 | Ph | Bn | 81 | 73 |
| 7 | Ph | *i*Bu | 83 | 87 |
| 8 | Ph | cyclopentyl | 86 | 84 |
| 9 | Ph | cyclohexyl | 94 | 90 |
| 10 | Ph | *i*Pr | 95 | 91 |
| 11 | *p*-anisyl | *i*Pr | 96 | 91 |
| 12 | *p*-$ClC_6H_4$ | *i*Pr | 92 | 90 |
| 13 | 3-thiophenyl | *i*Pr | 96 | 90 |

[a] All data are the average of two experiments. [b] Yield of isolated product. [c] The *ee* value was determined after a single recrystallization from isopropanol (overall yield: 71 %).

A plausible mechanism for this new nucleophile-catalyzed method for the synthesis of aza-β-lactams is illustrated in Figure 1. Interestingly, the configuration at the quaternary stereocenter is different from that produced in Staudinger reactions that are catalyzed by **1** [Eq. (3); Ts = 4-toluenesulfonyl],[8b] and which are believed to proceed through a similar pathway.[15]




(3)

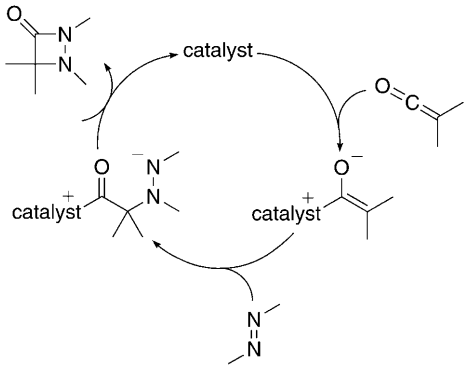



***Figure 1.*** Possible mechanism for the nucleophile-catalyzed synthesis of aza-β-lactams.

In conclusion, we have developed a new process, the nucleophile-catalyzed [2 + 2] cycloaddition of ketenes with azo compounds, to generate aza-β-lactams. In addition, we have established that planar-chiral PPY derivative **1** effects this convergent transformation to give good enantioselectivity, thereby providing the first catalytic asymmetric synthesis of this useful family of heterocycles.

## *Experimental Section*

General procedure: Solutions of the ketene (0.68 mmol) and dimethyl azodicarboxylate (100 mg, 0.68 mmol) in $CH_2Cl_2$ (49 mL), and of the catalyst (−)-**1** (13 mg, 0.035 mmol) in $CH_2Cl_2$ (0.8 mL) were prepared in a glove box. Following removal from the glove box, the solutions were cooled at −20 °C for 10 min, before the catalyst solution was added to the solution of ketene/dimethyl azodicarboxylate by syringe. After the reaction mixture was stirred for 2 h at −20 °C, the solvent was removed in vacuo and the residue was purified by column chromatography.

Received: May 25, 2008
Published online: July 30, 2008

**Keywords:** asymmetric catalysis · azo compounds · heterocycles · homogeneous catalysis · lactams

[1] For an example, see: H. Morioka, M. Takezawa, H. Shibai, T. Okawara, M. Furukawa, *Agric. Biol. Chem.* **1986**, *50*, 1757–1764.
[2] For leading references on the synthesis and utility of enantioenriched α,α-disubstituted α-amino acids, see: a) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569–623; b) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406–430.
[3] a) For leading references on the synthesis and utility of hydantoins, see: M. Meusel, M. Gütschow, *Org. Prep. Proced. Int.* **2004**, *36*, 391–443; b) phenytoin sodium and fosphenytoin, which serve as medications to treat epilepsy, are examples of bioactive hydantoins.
[4] For examples of methods for the synthesis of aza-β-lactams, see: a) L. S. Hegedus, B. R. Lundmark, *J. Am. Chem. Soc.* **1989**, *111*, 9194–9198; b) E. C. Taylor, N. F. Haley, R. J. Clemens, *J. Am. Chem. Soc.* **1981**, *103*, 7743–7752; c) G. Lawton, C. J. Moody, C. J. Pearson, *J. Chem. Soc. Perkin Trans. 1* **1987**, 899–902.
[5] K. Achiwa, S.-i. Yamada, *Tetrahedron Lett.* **1974**, *15*, 1799–1802.
[6] For a pioneering study, see: A. H. Cook, D. G. Jones, *J. Chem. Soc.* **1941**, 184–187.

[7] For references to early studies, see: a) G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542 – 547; for recent studies, see: b) E. C. Lee, K. M. McCauley, G. C. Fu, *Angew. Chem.* **2007**, *119*, 995 – 997; *Angew. Chem. Int. Ed.* **2007**, *46*, 977 – 979; c) X. Dai, T. Nakai, J. A. C. Romero, G. C. Fu, *Angew. Chem.* **2007**, *119*, 4445 – 4447; *Angew. Chem. Int. Ed.* **2007**, *46*, 4367 – 4369.

[8] a) E. C. Lee, B. L. Hodous, E. Bergin, C. Shih, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11586 – 11587; b) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578 – 1579.

[9] J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518 – 6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358 – 6360.

[10] For an overview on the chemistry of ketenes, see: T. T. Tidwell, *Ketenes*, Wiley-Interscience, New York, **2006**.

[11] For examples where phosphepine **3** is used as a chiral nucleophilic catalyst, see: a) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234 – 12235; b) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1454 – 1457; *Angew. Chem. Int. Ed.* **2006**, *45*, 1426 – 1429.

[12] For a review of the use of chiral amines as enantioselective nucleophilic catalysts, see: S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985 – 3012.

[13] Notes: a) dimerization of the ketene is sometimes observed as an undesired side reaction; b) the use of non-chlorinated solvents can lead to significant changes in enantioselectivity.

[14] Notes: a) use of diethyl, rather than dimethyl, azodicarboxylate for reactions of phenyl ethyl ketene and *p*-chlorophenyl isopropyl ketene led to 85% yield with 80% *ee* (see Table 2, entry 2) and 96% yield with 86% *ee* (see Table 2, entry 12), respectively; b) this method is not highly air- or moisture-sensitive: for a cycloaddition of phenyl ethyl ketene which was carried out in air and with unpurified $CH_2Cl_2$, a fairly good yield and *ee* value were observed (77% yield, 83% *ee*); c) a reaction conducted on 1 g of phenyl ethyl ketene proceeded in 77% yield with 84% *ee*; d) for the conversion of one of these aza-β-lactams into a hydantoin and an α,α-disubstituted amino acid, see the Supporting Information.

[15] Note: the *ee* value of the product correlates linearly with that of the catalyst. For a review of non-linear effects in asymmetric catalysis, see: H. B. Kagan, T. O. Luukas in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, Chapter 4.1.