Published in final edited form as:

Angew Chem Int Ed Engl. 2008 ; 47(37): 7048–7050. doi:10.1002/anie.200802439.

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

Jacob M. Berlin and Gregory C. Fu*

Keywords

asymmetric catalysis; azo compounds; homogeneous catalysis; heterocycles; ketenes; lactams

Although aza- β -lactams have attracted interest due to their biological activity[1] and to their utility as intermediates in organic chemistry (e.g., for the generation of α -amino acids[2] and of hydantoins[3]),[4] only limited progress has been described 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 (PPY = 4-(pyrrolidino)pyridine; e.g., **1** and **2**) as enantioselective catalysts for an array of transformations,[7] including couplings of ketenes with imines[8] and with aldehydes.[9,10] Although there are no reports of nucleophilic catalysis of [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. In this investigation, we establish that PPY derivative **1** can achieve the first catalytic asymmetric synthesis of aza- β -lactams, via [2+2] cycloadditions of ketenes with azo compounds [Eq. (2)].

**We thank Dr. Xing Dai, Dr. Maximilian Dochnahl, and Takashi Nakai for helpful discussions and for experimental assistance. Support has been provided by the NIH (National Institute of General Medical Sciences: R01-GM57034), Merck Research Laboratories, and Novartis.

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

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

(2)

As part of our initial study, we examined the cycloaddition of phenyl ethyl ketene with dimethyl azodicarboxylate (1.0 equiv). We were pleased to determine that planar-chiral PPY derivative **1** serves as an effective catalyst for the desired coupling, generating the aza- β -lactam in good ee and yield (Table 1, entry 1; in the absence of a catalyst, there is no reaction: entry 2). Under the same 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 (e.g., entries 3–5).[11,12] The substituents of the azo compound have a significant impact on the ee and the yield, with the methoxycarbonyl group affording the best results (entry 1 vs. entries 6–9). If $\text{ClCH}_2\text{CH}_2\text{Cl}$, rather than CH_2Cl_2 , is employed as the solvent, then formation of the aza- β -lactam proceeds less efficiently (entry 1 vs. entry 10). The reaction temperature of choice appears to be $-20\text{ }^\circ\text{C}$ (entry 1 vs. entries 11–12).[13]

The optimized conditions can be applied to the enantioselective synthesis of aza- β -lactams from a variety of ketenes (Table 2). If the alkyl group is small (Me or primary), the desired heterocycle is generally produced with good, not excellent, enantioselectivity (~85% ee; entries 1–7). Fortunately, the ee of the aza- β -lactams is readily enhanced by recrystallization (e.g., the product generated from phenyl ethyl ketene can be obtained in >99% ee after a single crystallization; see entry 2 of Table 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; entries 8–13).[14]

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 PPY derivative **1** [Eq. (3)],^[8b] which are believed to proceed through a similar pathway.[15]

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** achieves this convergent transformation with

good enantioselectivity, thereby providing the first catalytic asymmetric synthesis of this useful family of heterocycles.

Experimental Section

General procedure: In a glove box, a solution was prepared of the ketene (0.68 mmol) and dimethyl azodicarboxylate (100 mg, 0.68 mmol) in CH_2Cl_2 (49 mL). A solution was also prepared of catalyst (–)-**1** (13 mg, 0.035 mmol) in CH_2Cl_2 (0.8 mL). Both vessels were removed from the glove box and placed in a –20 °C bath. After 10 minutes, the solution of the catalyst was added by syringe to the solution of ketene and dimethyl azodicarboxylate. The reaction mixture was stirred for 2 hours at –20 °C, and then the solvent was removed and the residue was purified by column chromatography.

References

1. For example, see: Morioka H, Takezawa M, Shibai H, Okawara T, Furukawa M. *Agric Biol Chem* 1986;50:1757–1764.
2. For leading references to the synthesis and utility of enantioenriched α,α -disubstituted α -amino acids, see: a) Cativiela C, Diaz-de-Villegas MD. *Tetrahedron: Asymmetry* 2007;18:569–623. b) Vogt H, Bräse S. *Org Biomol Chem* 2007;5:406–430. [PubMed: 17252120]
3. For leading references to the synthesis and utility of hydantoins, see: Meusel M, Gütschow M. *Org Prep Proced Int* 2004;36:391–443. b) Phenytoin sodium and fosphenytoin, which serve as epilepsy medications, are examples of bioactive hydantoins.
4. For examples of methods for the synthesis of aza- β -lactams, see: a) Hegedus LS, Lundmark BR. *J Am Chem Soc* 1989;111:9194–9198. b) Taylor EC, Haley NF, Clemens RJ. *J Am Chem Soc* 1981;103:7743–7752. c) Lawton G, Moody CJ, Pearson CJ. *J Chem Soc, Perkin Trans 1* 1987:899–902.
5. Achiwa K, Yamada S-i. *Tetrahedron Lett* 1974;20:1799–1802.
6. For a pioneering study, see: Cook AH, Jones DG. *J Chem Soc* 1941:184–187.
7. For leading references to early studies, see: a) Fu GC. *Acc Chem Res* 2004;37:542–547. [PubMed: 15311953] For two recent investigations, see: b) Lee EC, McCauley KM, Fu GC. *Angew Chem, Int Ed* 2007;46:977–979. Dai X, Nakai T, Romero JAC, Fu GC. *Angew Chem, Int Ed* 2007;46:4367–4369.
8. a) Lee EC, Hodous BL, Bergin E, Shih C, Fu GC. *J Am Chem Soc* 2005;127:11586–11587. [PubMed: 16104719] b) Hodous BL, Fu GC. *J Am Chem Soc* 2002;124:1578–1579. [PubMed: 11853423]
9. Wilson JE, Fu GC. *Angew Chem, Int Ed* 2004;43:6358–6360.
10. For an overview of the chemistry of ketenes, see: Tidwell, TT. *Ketenes*. Wiley-Interscience; New York: 2006.
11. For previous examples of the use of phosphepine **3** as a chiral nucleophilic catalyst, see: a) Wurz RP, Fu GC. *J Am Chem Soc* 2005;127:12234–12235. [PubMed: 16131196] b) Wilson JE, Fu GC. *Angew Chem, Int Ed* 2006;45:1426–1429.
12. For a review of the use of chiral amines as enantioselective nucleophilic catalysts, see: France S, Guerin DJ, Miller SJ, Lectka T. *Chem Rev* 2003;103:2985–3012. [PubMed: 12914489]
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 80% ee/85% yield (cf. entry 2 of Table 2) and 86% ee/96% yield (cf. entry 12 of Table 2), respectively. b) This method is not highly air- or moisture-sensitive: for a cycloaddition of phenyl ethyl ketene that was set up in the air with unpurified CH_2Cl_2 , fairly good ee and yield were observed (83% ee, 77% yield). c) A reaction conducted on 1 g of phenyl ethyl ketene proceeded in 84% ee and 77% yield. 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. Notes: a) We speculate that the dichotomy may be due to different stereochemistry-determining steps for the two processes. b) Product ee correlates linearly with catalyst ee. For a review of non-linear

effects in asymmetric catalysis, see: Kagan, HB.; Luukas, TO. Chapter 4.1. In: Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. *Comprehensive Asymmetric Catalysis*. Springer; New York: 1999.

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

Table 1Nucleophile-catalyzed enantioselective synthesis of aza- β -lactams: Effect of reaction parameters.

Entry	Change from the "standard" conditions	ee (%)	Yield (%)
1	none	86	89
2	no (-)-1	–	<5
3	(-)-2, instead of (-)-1	-15	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>i</i> Pr	32	81
8	R = CO ₂ CH ₂ CCl ₃	20	20
9	R = CO(piperidinyl)	–	<5
10	ClCH ₂ CH ₂ Cl, instead of CH ₂ Cl ₂	87	65
11	-30 °C	85	68
12	-10 °C	73	68

A negative ee value signifies that the opposite enantiomer of the product is formed preferentially.

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

entry	Ar	alkyl	ee (%)	yield (%) ^[a]
1	Ph	Me	85	53
2	Ph	Et	86 (>99 ^[b])	89
3	<i>m</i> -tolyl	Et	85	79
4	<i>o</i> -tolyl	Et	67	46
5	<i>o</i> -anisyl	Et	93	89
6	Ph	Bn	81	73
7	Ph	<i>i</i> Bu	83	87
8	Ph	cyclopentyl	86	84
9	Ph	cyclohexyl	94	90
10	Ph	<i>i</i> Pr	95	91
11	<i>p</i> -anisyl	<i>i</i> Pr	96	91
12	<i>p</i> -ClC ₆ H ₄	<i>i</i> Pr	92	90
13	3-thiophenyl	<i>i</i> Pr	96	90

All data are the average of two experiments.

^[a] Isolated yield.^[b] ee after one crystallization from isopropanol (overall yield: 71%).