Asymmetric Catalysis

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

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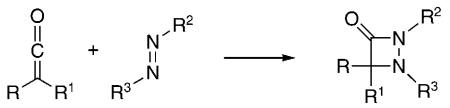
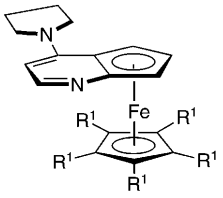
Even though aza-β-lactams have attracted interest because of their biological activity[1] and their utility as intermediates in organic chemistry (e.g., for the generation of α-amino acids and hydantoins),[2–4] only limited progress has been reported with regard to the enantioselective synthesis of this 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.



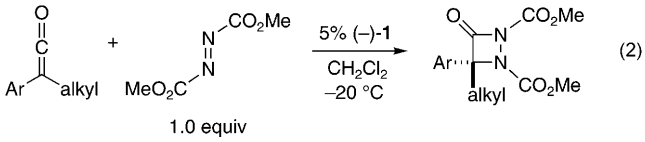
(1)

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**

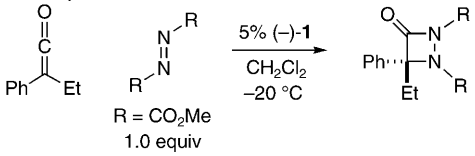
Initially, we examined the cycloaddition of phenyl ethyl ketene with dimethyl azodicarboxylate (1.0 equiv). We found that the planar-chiral PPY derivative **1** serves as an effective catalyst for the desired coupling, and generates the aza-β-lactam in good yield and enantioselectivity (Table 1, entry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



1.0 equiv

(2)

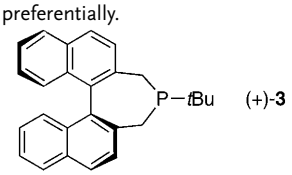
Table 1: Effect of changing the "standard" reaction conditions (outlined in the equation below) in the nucleophile-catalyzed enantioselective synthesis of aza-β-lactams.



R = CO_2Me
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_2Et	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

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$ClCH_2CH_2Cl$ 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]

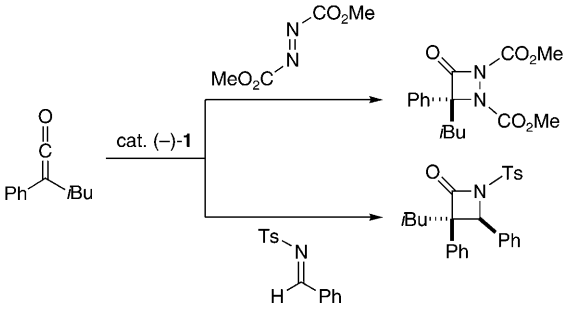
The optimized reaction conditions can be applied to the enantioselective synthesis of aza-β-lactams when starting from a variety of ketenes (Table 2). If the alkyl group is small (i.e., Me or a primary substituent), then the desired heterocycle is generally produced with good (but not excellent) enantioselectivity (≈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)

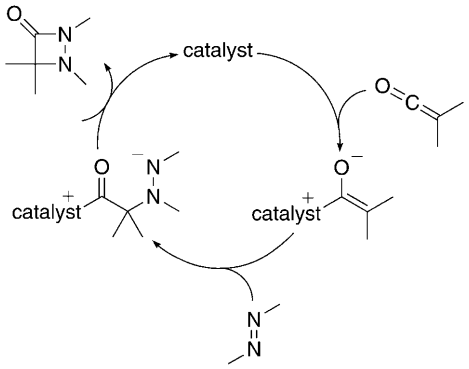


Figure 1. Possible mechanism for the nucleophile-catalyzed synthesis of aza-β-lactams.

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.

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[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.
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[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.

