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Published on Web 02/01/2002

Enantioselective Staudinger Synthesis of β-Lactams Catalyzed by a Planar-Chiral Nucleophile[1]

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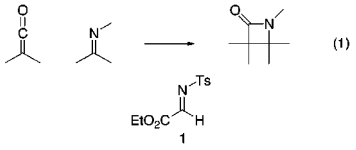
Received October 25, 2001

The development of efficient methods for the stereoselective generation of β-lactams is an important goal, due to their utility as synthetic intermediates and to their biological activity.[2] Currently, an array of widely used antibiotics are based on the β-lactam subunit (e.g., penicillins and cephalosporins). During recent years, however, the need for *new* β-lactam (and other) antibiotics has been growing, as a consequence of the emergence of strains of bacteria that are resistant to existing drugs.[3] In addition to their significance as targets for medicinal chemistry, enantiopure β-lactams also serve as versatile chiral building blocks in organic synthesis. The commercial semisynthesis of the anticancer agent paclitaxel (Taxol), which is produced from a protected baccatin III through reaction with a β-lactam to install the β-amino acid-derived side chain, represents one particularly prominent example of this latter role.[4]

The Staudinger reaction, an overall [2 + 2] cycloaddition of a ketene with an imine, provides an efficient, convergent route to β-lactams (eq 1).[5] Although a number of chiral auxiliary-based asymmetric Staudinger processes have been described,[5b] only one investigation of enantioselective catalysis of this transformation has been reported.[6,7] In that study, Lectka demonstrated that, using a quinine derivative as the catalyst, highly stereoselective coupling of a range of monosubstituted ketenes, as well as one symmetrical disubstituted ketene, could be achieved; on the other hand, only one imine (**1**) was shown to be a suitable reaction partner.



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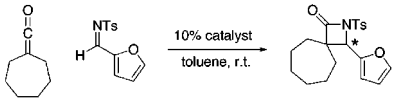
Several years ago, we initiated a program focused on the application of planar-chiral heterocycles (e.g., **2**−**6**) as catalysts for asymmetric reactions of ketenes. As one part of this investigation, we determined that azaferrocene **2** catalyzes the enantioselective addition of alcohols to ketenes.[8] In this report, we describe a second application of planar-chiral heterocycles to reactions of ketenes; specifically, in work that complements the pioneering study of Lectka, we establish that PPY (PPY = 4-(pyrrolidino)pyridine) derivative **6** is an effective catalyst for the asymmetric Staudinger reaction of symmetrical and unsymmetrical disubstituted ketenes with a range of imines, furnishing the target β-lactams with very good stereoselection.

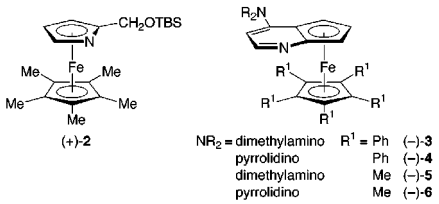
In our initial investigation of the Staudinger reaction, we surveyed the planar-chiral heterocycles (**2**−**6**) that we have found to be most useful for other nucleophile-catalyzed processes.[9] As illustrated in Table 1, for the coupling of hexamethyleneketene with *N*-(2-furfurylidene)-4-methylbenzenesulfonamide, azaferrocene **2** is ineffective (entry 1). Similarly, FeC_5Ph_5-bound planar-chiral pyridine derivatives **3** and **4** provide essentially racemic product (entries 2 and 3). Fortunately, however, both of the FeC_5Me_5-derived catalysts (**5** and **6**) afford the desired β-lactam in good enantiomeric excess (85% ee; entries 4 and 5).

Table 1. Comparison of the Effectiveness of Planar-Chiral Heterocycles as Catalysts for the Staudinger Synthesis of β-Lactams



entry	catalyst	ee (%)[a]	entry	catalyst	ee (%)[a]
1	(−)-**2**	<5	4	(+)-**5**	**85**
2	(+)-**3**	<5	5	(−)-**6**	**85**
3	(−)-**4**	<5			

[a] Average of two runs.



On the basis of these observations, we chose to focus our attention on asymmetric Staudinger reactions catalyzed by PPY derivative **6**, and we were pleased to discover that this complex efficiently couples hexamethyleneketene with a diverse set of imines (Table 2, entries 1−5).[10] Thus, imines derived from aromatic (entries 1 and 2), α,β-unsaturated (entry 3), and aliphatic (entries 4 and 5) aldehydes undergo cycloaddition in uniformly good-to-excellent enantioselectivities and yields. Relative to prior work on catalytic asymmetric Staudinger reactions, the broad scope with respect to the imine component is noteworthy, especially the challenging, readily enolizable imine depicted in entry 5.[11] With regard to the ketene component, not only cyclic, but also acyclic, symmetrical disubstituted ketenes are suitable substrates (entries 6−7).[12]

In the case of catalytic asymmetric Staudinger reactions of imines with *un*symmetrical disubstituted ketenes, we need to control not only enantioselectivity but also diastereoselectivity. We have determined that PPY derivative **6** is in fact an effective catalyst for reactions of this family of ketenes, furnishing two new contiguous (one quaternary[13] and one tertiary) stereocenters with very good stereoselection and yield (Table 3). As with symmetrical ketenes, catalyst **6** is versatile, coupling a range of unsymmetrical ketenes and imines with comparatively little variation in stereoselectivity.[14] We believe that Staudinger reactions catalyzed by **6** proceed through the pathway outlined in Figure 1.[6]

As noted earlier, interest in the synthesis of enantiopure β-lactams derives in part from their potential utility as chiral building blocks.[2]

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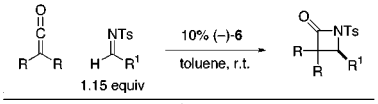
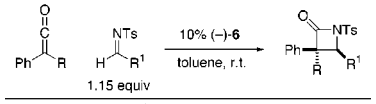
Table 2. Catalytic Enantioselective Staudinger Reactions of Symmetrical Disubstituted Ketenes with a Range of Imines



Entry	R	R^1	ee (%)[a]	Yield (%)[a]
1	$-(CH_2)_6-$	-Ph	81	84
2	$-(CH_2)_6-$	2-furyl	92	90
3	$-(CH_2)_6-$	-CH=CHPh	91	82
4	$-(CH_2)_6-$	cyclopropyl	94	89
5[b]	$-(CH_2)_6-$	cyclohexyl	94	76
6[c]	Et	2-furyl	92	93
7[c]	Et	-CH=CHPh	92	83

[a] Average of two runs. [b] Reaction was started at −40 °C. [c] Reaction was run at 35 °C in 1:1 toluene/THF with 1.5 equiv of ketene.

Table 3. Catalytic Enantioselective Staudinger Reactions of Unsymmetrical Disubstituted Ketenes with a Range of Imines



Entry	R	R^1	dr[a]	ee (%)[a]	Yield (%)[a]
1	*i*-Bu	-Ph	8:1	98	88
2	*i*-Bu	2-furyl	11:1	98	97
3	*i*-Bu	-CH=CHPh	10:1	98	95
4	*i*-Bu	cyclopropyl	15:1	89	88
5	Et	2-furyl	9:1	95	97
6	Et	cyclopropyl	10:1	98	98

[a] Average of two runs.

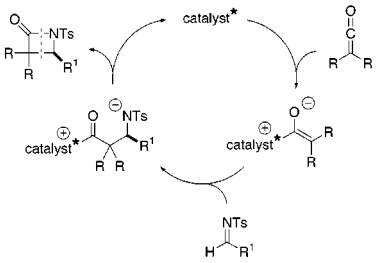
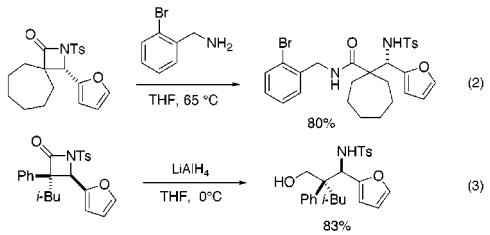


Figure 1. Proposed mechanism for enantioselective Staudinger reactions catalyzed by PPY derivative **6**.

We have established that the β-lactams generated by our catalytic asymmetric Staudinger reactions can be ring-opened with amines to afford β-amino amides (eq 2) and with $LiAlH_4$ to furnish *N*-protected γ-amino alcohols (eq 3). As expected, the enantiomeric and diastereomeric purity of the β-lactam is preserved during these transformations.



In summary, we have demonstrated that a planar-chiral derivative of PPY is an excellent catalyst for enantioselective Staudinger reactions. A range of symmetrical and unsymmetrical disubstituted ketenes couple with a wide array of imines to provide β-lactams with very good stereoselection and yield; this work represents a considerable expansion in the scope of this important process. Current efforts are focused on exploring the breadth and the mechanism of this and related nucleophile-catalyzed asymmetric reactions of ketenes.

Acknowledgment. We thank Ivory D. Hills for assistance with X-ray crystallography. Support has been provided by Bristol-Myers Squibb, Merck, the National Institutes of Health (National Institute of General Medical Sciences, R01-GM57034), Novartis, and Pfizer.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832. The yield of β-lactam, based on the acid chloride precursor to the ketene, ranges from 36 to 65% (six examples). See also: Wack, H.; Drury, W. J., III; Taggi, A. E.; Ferraris, D.; Lectka, T. *Org. Lett.* **1999**, *1*, 1985−1988.

(7) For four other methods for the catalytic enantioselective synthesis of β-lactams, see: (a) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931−934. (b) Watanabe, N.; Anada, M.; Hashimoto, S.-i.; Ikegami, S. *Synlett* **1994**, 1031−1033. Doyle, M. P.; Kalinin, A. V. *Synlett* **1995**, 1075−1076. (c) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999−5004. (d) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060−2061. Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715−716. Unfortunately, none of these methods is general and highly enantioselective.

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(9) (a) For an overview, see: Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. (b) For more recent work, see: Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234−236.

(10) Optimization (e.g., of concentration) of the initial reaction conditions led to improved enantioselectivity (Table 1, entry 5 vs Table 2, entry 2).

(11) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75−77.

(12) Generation of diethylketene proceeds more cleanly in toluene/THF than in toluene alone; therefore, the Staudinger reactions of this substrate were run in toluene/THF (Table 2, entries 6 and 7).

(13) For a recent review of catalytic asymmetric methods that generate quaternary stereocenters, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. See also: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(14) (a) Under otherwise identical conditions, in the absence of catalyst, no β-lactam is generated. (b) Almost identical stereoselectivity is observed with 1% catalyst, but the rate of product formation is very slow. (c) Approximately 80% of the catalyst can be recovered at the end of the reaction. (d) Phenylmethylketene reacts with *N*-(2-furfurylidene)-4-methylbenzenesulfonamide to give the β-lactam product with dr = 2: 1 (major diastereomer: 84% ee).

JA012427R