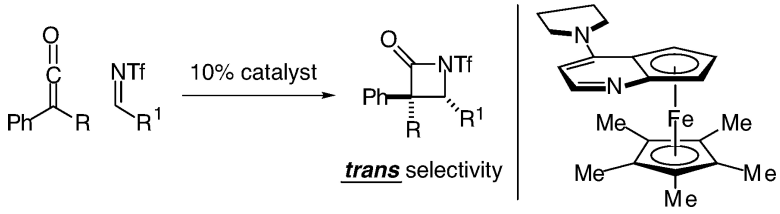
Communication

Catalytic Asymmetric Staudinger Reactions to Form β-Lactams: An Unanticipated Dependence of Diastereoselectivity on the Choice of the Nitrogen Substituent

Elaine C. Lee, Brian L. Hodous, Enda Bergin, Crystal Shih, and Gregory C. Fu

J. Am. Chem. Soc., **2005**, 127 (33), 11586-11587• DOI: 10.1021/ja052058p • Publication Date (Web): 30 July 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 21 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 07/30/2005

Catalytic Asymmetric Staudinger Reactions to Form β-Lactams: An Unanticipated Dependence of Diastereoselectivity on the Choice of the Nitrogen Substituent

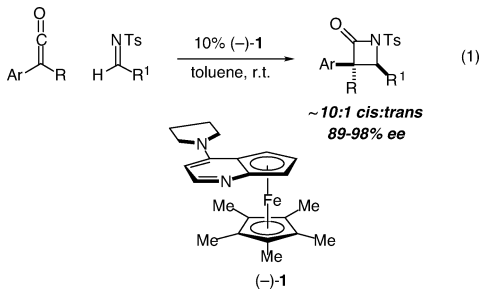
Elaine C. Lee, Brian L. Hodous, Enda Bergin, Crystal Shih, and Gregory C. Fu*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received March 31, 2005; E-mail: gcf@mit.edu

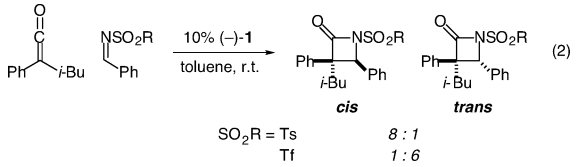
Long before the biological activity[1] or the synthetic utility[2] of β-lactams was appreciated, Staudinger developed the first method for their synthesis by coupling a ketene with an imine.[3] This convergent strategy has endured as a particularly attractive approach to generating this important family of compounds.[4] In the case of Staudinger reactions of monosubstituted ketenes, which have been intensively studied, the cis β-lactam is typically the predominant product.[5] If the trans diastereomer is desired, it can be accessed through epimerization of the cis isomer under basic conditions.

Staudinger reactions of disubstituted ketenes are much less common,[4] despite the fact that β-lactams that bear two α substituents are an important class of target molecules.[6] Only one method has been described for the diastereo- and enantioselective synthesis of α,α-disubstituted β-lactams through a catalytic asymmetric Staudinger reaction (eq 1);[7,8] as indicated, this process preferentially affords the cis isomer.[9] Of course, for such β-lactams, the trans diastereomer cannot be generated from the cis isomer through simple base-induced epimerization. Therefore, for α,α-disubstituted β-lactams, it is necessary to develop a Staudinger reaction that is itself trans selective. In this report, we describe the achievement of this objective.



(1)

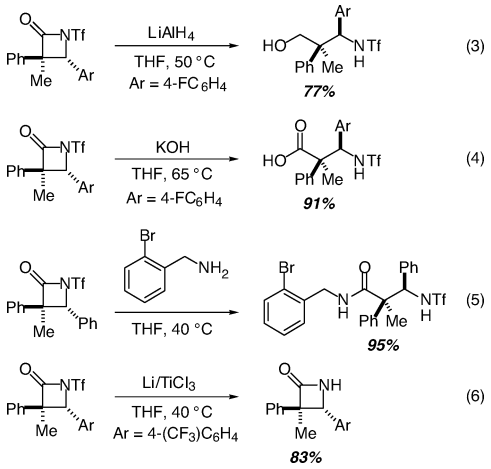
While attempting to improve upon the process illustrated in eq 1, we made the exciting discovery that the cis/trans selectivity of Staudinger reactions catalyzed by PPY derivative **1** (PPY = 4-(pyrrolidino)pyridine) can be effectively controlled through the appropriate choice of the N-protecting group of the imine. Thus, ketenes couple with *N*-tosyl imines to predominantly generate cis β-lactams, whereas reactions with *N*-triflyl imines preferentially furnish the trans isomers (e.g., eq 2)!



(2)

Aware of the paucity of methods for the catalytic asymmetric synthesis of β-lactams,[10] we decided to optimize and to investigate the scope of this interesting new trans-selective Staudinger reaction, which produces two adjacent stereocenters (one all-carbon quaternary[11] and one tertiary). We were pleased to determine that a range of ketenes and *N*-triflyl imines couple to furnish an array of β-lactams not only with generally good trans *diastereoselectivity* but also with useful *enantioselectivity* (Table 1, entries 1−9).[12] In addition, we have examined one coupling of a *symmetrical* disubstituted ketene (entry 10); gratifyingly, the desired β-lactam is generated in excellent enantiomeric excess (98%).

As mentioned earlier, β-lactams are interesting targets due not only to their bioactivity but also to their utility as precursors to other important families of compounds. To the best of our knowledge, only one report has described the synthesis of an *N*-triflyl β-lactam,[13] and there have been no investigations of their reactivity. We have established that a range of derivatizations of *N*-triflyl β-lactams can be achieved in good yield without an erosion in stereochemical purity, furnishing protected γ-amino alcohols, β-amino acids, and β-amino amides (eqs 3−5). Furthermore, the triflyl group can be reductively removed (eq 6).[14]



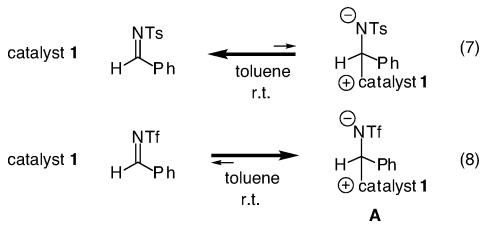
(3)

(4)

(5)

(6)

Naturally, we were intrigued by the remarkable dependence of the cis/trans diastereoselectivity on the choice of the *N*-sulfonyl group (eq 2). Interestingly, the differing electrophilicity of the imines leads to divergent behavior in the presence of catalyst **1**; whereas there is no evidence by ^{1}H NMR of an interaction between the catalyst and an *N*-tosyl imine (eq 7), the catalyst reacts quantitatively with an *N*-triflyl imine to furnish adduct **A** (eq 8).[15]



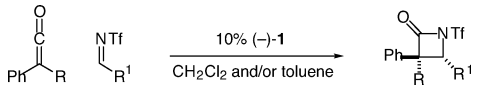
(7)

(8)

It is tempting to suggest that the origin of the different cis/trans preferences for Staudinger reactions of *N*-tosyl/triflyl imines catalyzed by **1** may lie in the divergent reactivity depicted in eqs 7 and 8, that is, that these two classes of imines couple with ketenes by

10.1021/ja052058p CCC: $30.25

Table 1. Catalytic Asymmetric Synthesis of Highly Substituted trans β-Lactams[a]



entry	R	R[1]	trans:cis	ee (%)[b]	yield (%)[c]
1	Et	Ph	86:14	63	60
2	Me	Ph	98:2	81	83
3	*i*-Bu	Ph	97:3	63	72
4	Me	4-FC_6H_4	96:4	85	84
5	Me	4-$(CF_3)C_6H_4$	97:3	69	80
6	Me	4-$(OMe)C_6H_4$	81:19	82	76
7	Me	*o*-tolyl	81:19	99	89
8	Me	2-BrC_6H_4	80:20	84	79
9	Me	2-naphthyl	98:2	94	76
10	Ph	Ph	-	98	62

[a] All data are the average of two experiments. [b] Enantiomeric excess of the trans diastereomer. [c] Yield of the mixture of diastereomers.

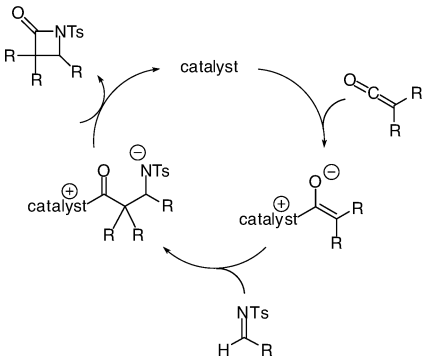


Figure 1. A mechanism for nucleophile-catalyzed Staudinger reactions: a "ketene-first" pathway.

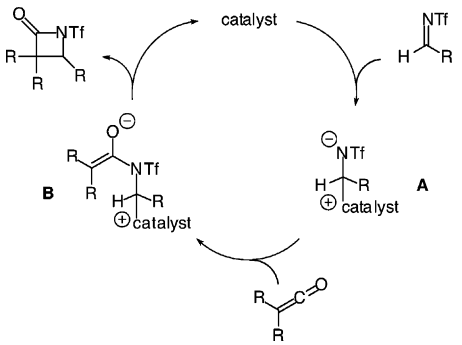


Figure 2. A mechanism for nucleophile-catalyzed Staudinger reactions: an "imine-first" pathway.

distinct mechanisms. Lectka has proposed that Staudinger reactions of *N*-tosyl imines catalyzed by a quinine derivative proceed through the pathway illustrated in Figure 1,[8] and we believe that this is the mechanism for reactions of *N*-tosyl imines catalyzed by **1**. One speculative suggestion is that *N*-triflyl imines, on the other hand, react through the pathway outlined in Figure 2, wherein adduct **A** of eq 8 serves as an intermediate. We are currently pursuing experiments designed to test this as well as other possible explanations for the striking dependence of diastereoselectivity on the N-protecting group.[16]

In conclusion, relatively few methods have been described for the catalytic asymmetric synthesis of β-lactams, and those that have been reported are typically cis selective. In this investigation, we have developed the first catalytic enantioselective Staudinger reactions that provide trans β-lactams. Interestingly, the key to this method is the use of an *N*-triflyl protecting group for the imine. We have suggested that the unusual trans diastereoselectivity may be the consequence of a novel pathway for Staudinger reactions of this class of highly electrophilic imines. We have demonstrated that, along with serving as interesting targets in their own right, *N*-triflyl β-lactams readily react with nucleophiles to generate other useful families of compounds, including γ-amino alcohols and β-amino acids. Additional synthetic and mechanistic studies of catalytic asymmetric Staudinger reactions are underway.

Acknowledgment. We thank Dr. Peter Mueller and Dr. Ivory D. Hills for X-ray crystallographic assistance, and Dr. Kevin M. McCauley for a preliminary NMR study. Support has been provided by the NIH (National Institute of General Medical Sciences: R01-GM57034; National Cancer Institute: Training Grant CA009112), Merck, and Novartis.

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.

References

(1) For leading references, see: (a) *The β-Lactamases: A Major Cause of Resistance of β-Lactam Antibiotics and β-Lactamase Inhibitors*; Mascaretti, O. A., Ed.; Bentham: Hilversum, Netherlands, 1999. (b) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Chapters 1.18−1.20. (c) *Chemistry and Biology of Beta-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vols. 1−3.

(2) For leading references, see: (a) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921−1949. (b) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889−1920. (c) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631−7649. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813−1826.

(3) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51−123.

(4) For reviews of the Staudinger reaction, see: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837−1872. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235. (c) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; pp 295−368.

(5) For leading references to uncommon trans-selective processes, see: (a) Liang, Y.; Jiao, L.; Zhang, S.; Xu, J. *J. Org. Chem.* **2005**, *70*, 334−337. (b) ref 4b.

(6) For example, see: (a) Kende, A. S.; Liu, K.; Kaldor, I.; Dorey, G.; Koch, K. *J. Am. Chem. Soc.* **1995**, *117*, 8258−8270. (b) Sandanayaka, V. P.; Prashad, A. S.; Yang, Y.; Williamson, R. T.; Lin, Y. I.; Mansour, T. S. *J. Med. Chem.* **2003**, *46*, 2569−2571.

(7) (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578−1579. (b) In addition, Lectka has described a catalytic asymmetric Staudinger reaction of a symmetrical disubstituted ketene (for which there is no issue of diastereoselectivity): Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(8) For pioneering studies of catalytic asymmetric Staudinger reactions, see: (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832. (b) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206−1215 and references therein.

(9) We use the terms cis and trans as a shorthand means of describing the position of the C3 aryl group relative to the C4 substituent.

(10) For leading references, see: (a) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592−600. (b) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377−4379.

(11) For leading references to methods for the synthesis of all-carbon quaternary stereocenters, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146.

(12) Notes: (a) The stereoselectivity is sensitive to the choice of reaction temperature (−78 °C to room temperature) and solvent (CH_2Cl_2 and/or toluene). (b) Under identical conditions, but in the absence of catalyst, no β-lactam is produced. (c) If desired, the catalyst can generally be recovered in >70% yield.

(13) Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dahlgren, M. E. *Tetrahedron* **1990**, *46*, 2255−2262.

(14) For the use of this reagent to remove a Ts group from a sulfonamide, see: Nayak, S. K. *Synthesis* **2000**, 1575−1578.

(15) For an X-ray crystal structure of **A**, see the Supporting Information.

(16) Some preliminary observations: (1) On the basis of a ^1H NMR study, we believe that the resting state of the catalyst during Staudinger reactions of *N*-triflyl imines may be adduct **B** (Figure 2). (2) An initial kinetics investigation indicates that (a) the rate law is first-order in catalyst and zero-order in ketene and imine; (b) there is a substantial normal α secondary kinetic isotope effect for reactions of undeuterated versus monodeuterated imines.

JA052058P