Diastereoselective Synthesis of *trans*-β-Lactams Using a Simple Multifunctional Catalyst

Ciby J. Abraham,[1] Daniel H. Paull, Cajetan Dogo-Isonagie,[2] Thomas Lectka*

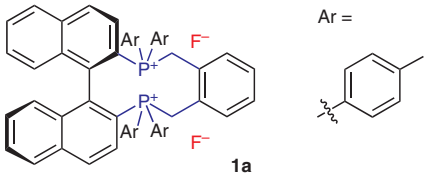
Department of Chemistry, New Chemistry Building, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, USA
Fax +1(410)5168420; E-mail: lectka@jhu.edu

Received 9 March 2009

Abstract: A catalytic, highly diastereoselective process for the synthesis of *trans*-β-lactams is reported. This system is based on a phosphonium fluoride precatalyst that both activates the nucleophile and directs the reaction process for high yield and diastereoselectivity.

Key words: *trans*-β-lactam, diastereoselectivity, cycloaddition, catalysis, imine, ketene acetal, phosphonium fluoride precatalyst

The synthesis of *trans*-disubstituted β-lactams can be a capricious process. Unpredictable mixtures of diastereomers often result, whereas reliable predictive models are in short supply. This is regrettable as the *trans*-diastereomers are every bit as useful as the *cis*; from antibiotics[3] to inhibitors of prostate-specific antigen[4] and cytomegalovirus protease,[5] the *trans*-isomers possess potent biological activity as well.[6] The most common method to synthesize *trans*-β-lactams employs the venerable Staudinger reaction,[7] which usually affords predominately the *cis*-diastereomer, although altering the nature of the substrates and reaction conditions can often promote the formation of *trans*-isomer.[6] From our standpoint, a reliable, easy to execute, and highly selective synthesis of *trans*-β-lactams would be a desirable contribution to the literature.[8] In this communication, we illustrate a strategy for the highly diastereoselective *trans*-β-lactam synthesis using imines, silyl ketene acetals,[9] and a phosphonium fluoride precatalyst. Diastereomeric ratios exceed 28:1 in all cases, and chemical yields are excellent.

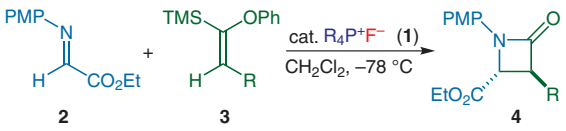


1a

Figure 1 New, highly diastereoselective precatalyst for the [2+2] cycloaddition reaction of silyl ketene acetals with α-imino esters

Interestingly, the *trans*-diastereomer is usually more thermodynamically stable than the *cis*, yet the *cis* is almost always formed in catalytic reactions because of a kinetically more favorable transition state (TS).[6] Presumably, a TS that produces the *trans*-diastereomer would therefore necessitate different conditions. In the reaction of cinchona alkaloid-derived ketene enolates with imines, for instance, the presence or absence of various metal cocatalysts has little or no effect on the diastereoselectivity of the highly *cis*-selective β-lactam forming reaction.[10] In these bifunctional reactions, even minor changes in the Lewis acid behavior could, in theory, reorganize the TS; therefore, when none of the many Lewis acids tested were able to provide a *trans*-selective reaction, we realized that more drastic changes were needed. After many calculations and laboratory tests, we found that an internally bifunctional nucleophilic catalyst, which contains a remote non-nucleophilic anion, helps to reorganize the usually *cis*-favoring TS to a *trans*-favored TS in the reaction of ketenes with imines.[8e] With this new insight in mind, we sought a new reaction manifold.

Having successfully made use of aryl ester-derived ketene acetals as nucleophilic ketene equivalents in a catalytically activated, *trans*-selective cycloaddition reaction with *o*-quinone methides (*o*-QM),[11] we noted these ketene acetals would provide excellent β-lactam precursors in a reaction with electrophilic imines.[12] We were encouraged by a report by Mukaiyama that α-aryl imines form *trans*-β-lactams in cycloaddition with silyl ketenethioacetals.[8b]



2 3 4

Scheme 1 *Trans*-β-lactams from ketene acetals and imines. PMP = *para*-methoxyphenyl

Initial efforts to catalyze the [2+2] β-lactam forming cycloaddition employed the ammonium fluoride precatalysts that worked well in the quinone methide cyclizations.[11] However, these tests resulted in poor yield and low, unpredictable diastereoselectivity. Reasoning that the ammonium catalyst did not allow for proper TS organization, we sought a phosphonium salt that could act as a Lewis acid, organizing the TS. To our satisfaction, aryl and alkyl phosphonium fluoride precatalysts generally gave good yields and diastereomeric ratios (dr) in favor of the *trans*-isomer. Catalyst optimization led us to a new phosphonium fluoride (**1a**, Figure 1) that was made by

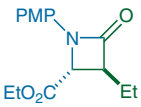
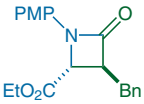
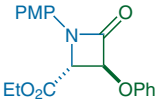
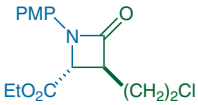
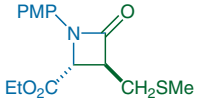
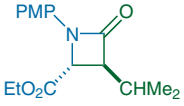
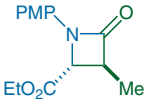
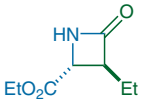
SYNLETT 2009, No. 10, pp 1651–1654
Advanced online publication: 02.06.2009
DOI: 10.1055/s-0029-1217348; Art ID: Y01309ST

counterion exchange of the bis-salt formed from (*R*)-tol-BINAP and *o*-xylene dibromide. A test reaction using this catalyst at 5 mol% loading provided β-lactam **4a** in 78% yield and 86:1 dr; the best diastereoselectivity of any of our catalyst tests (Scheme 1). Somewhat surprisingly, tetraphenylphosphonium fluoride (**1b**) provided nearly as good results as catalyst **1a**, and, in light of its lower cost and more facile preparation, it was used to test the method further.[13]

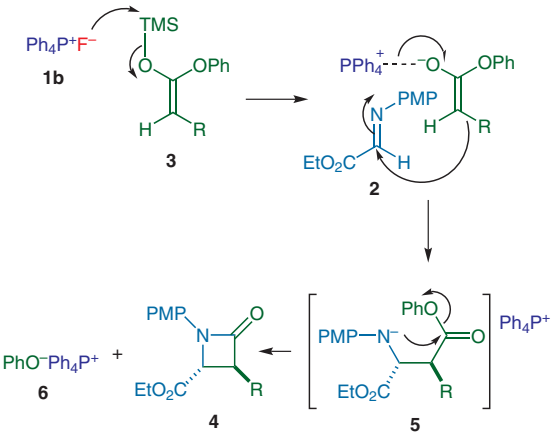
Several ketene acetals were screened to ensure that we had a consistently *trans*-diastereoselective β-lactam producing cycloaddition reaction with PMP-imine (**2**; Table 1). A variety of functional groups were well tolerated, including several different positions of hetero atoms and aryl groups, as well as branched aliphatics and heavy atoms such as chlorine and sulfur. The yields were good (83% on average) and the dr was excellent (60:1, *trans*/*cis* on average).

The reaction proceeds well with the phosphonium fluoride precatalyst (**1**). The catalyst functions to make a better nucleophile of the ketene acetal by nucleophilic attack on the silane. The second function of the catalyst, in its role as counterion to the enolate, perhaps is more important. The bulk of the phosphonium cation was essential for high diastereoselectivity; a change to various ammonium cations, for instance TBAF or other precatalysts that served well in the *o*-QM cyclization reactions, provided β-lactams in unsatisfactory yield and dr. The phosphonium cation is able to organize a TS in such a way that the *trans*-diastereomer is kinetically favored, whereas the ammonium cation is unable to make the reaction work well. The large phosphonium cation forces a *trans*-relationship of the substituents (Scheme 2).[14]

Table 1 *trans*-β-Lactams from the [2+2] Cycloaddition of **2** and **3** with 10 mol% PPh_4F (**1b**)

Entry	Product		dr (*trans*/*cis*)	Yield (%)
1		**4a**	78:1	82
2		**4b**	45:1	87
3		**4c**	88:1	88
4		**4d**	86:1	91
5		**4e**	38:1	84
6		**4f**	28:1	81
7		**4g**	51:1	71
8		**7a**	>99:1[a]	95[a]

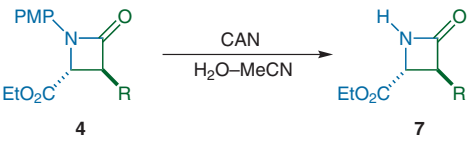
[a] Reaction of purified **4a** with CAN/H_2O.



Scheme 2 Proposed mechanism of *trans*-diastereoselective reaction

The mechanism of catalyst turnover is interesting as well. The precatalyst acts to initiate the reaction because of the high affinity of the fluoride ion for the TMS group of the silyl ketene acetal **3**. Once the reaction is initiated in this manner, it proceeds smoothly to completion. We believe that the eventual catalyst is the phosphonium phenoxide (**6**) that is likely formed in the rapid cyclization step shown as **5**. This is the most probable mechanism because we do not see any open, *N*-silylated product, even before workup.[15] In addition, Mukaiyama found that a complimentary *trans*-β-lactam forming cycloaddition was catalyzed by phenoxide.[8b]

Making this method more synthetically useful, the *para*-methoxyphenyl (PMP) protection is cleaved from the nitrogen without appreciable loss of yield or dr by reaction with cerium(IV) ammonium nitrate (CAN) in an acetonitrile/water mix (Scheme 3). For example, when an aqueous solution of CAN was added to lactam **4a** in acetonitrile at –10 °C, a high yield of deprotected lactam **7a** was afforded without loss of dr (Table 1, entry 8).



Scheme 3 Simple derivatization of lactam products

In conclusion, we have demonstrated a highly *trans*-selective β-lactam forming system in which a [2+2] cycloaddition between silyl ketene acetals and imines is promoted by a phosphonium fluoride precatalyst. The nature of the catalyst is important to the *trans*-selectivity and yield, which we believe are based on the phosphonium cation's ability to act as a Lewis acid. A mechanistic study to elucidate the mechanism of catalysis is forthcoming.

All reactions were carried out under anhydrous, air-free conditions using dried and distilled solvents. NMR data was collected on a 400 MHz (^{1}H) instrument, and ppm (δ) are given with respect to internal TMS or residual chloroform standards. Diastereomeric ratios were determined by comparison of integration of the C-2 ring proton of the *trans* and *cis*-diastereomers in the ^{1}H NMR prior to purification. PMP imine **2**[16] and silyl ketene acetals **3**[17] were prepared according to known procedures. Phosphonium fluoride catalysts were prepared from the corresponding phosphonium bromide by ion exchange.[18]

Representative Procedure for Ethyl *trans*-3-Ethyl-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (4a)[16]

PMP imine **2** (0.48 mmol) and tetraphenylphosphonium fluoride (**1b**; 0.048 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to –78 °C. Ketene acetal **3** (0.576 mmol), as a solution in CH_2Cl_2 (1 mL), was added to the reaction mixture dropwise. The reaction was allowed to warm to r.t. overnight. A sat. soln of NaF (3 mL) was added to the reaction, which was stirred at r.t. for 30 min. The organic layer was dried using $MgSO_4$ and purified by column chromatography (EtOAc–hexanes) to obtain the pure β-lactam. Yield: 82%; light-yellow residue; dr (*trans*/*cis*) = 78:1. ^{1}H NMR ($CDCl_3$): δ = 7.25 (d, 2 H), 6.89 (d, 2 H), 4.31 (q, 2 H), 4.21 (d, 1 H), 3.75 (s, 3 H), 3.26 (m, 1 H), 1.92–1.75 (m, 2 H), 1.55 (t, 3 H), 1.52 (t, 3 H). ^{13}C NMR ($CHCl_3$): δ = 170.1, 165.6, 156.3, 131.2, 117.8, 114.5, 61.8, 57.1, 56.6, 55.5, 21.7, 14.1, 11.2. IR (CH_2Cl_2): 1751, 1748 cm^{-1}.

Ethyl *trans*-3-Benzyl-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (4b)

Yield: 87%; light-yellow residue; dr (*trans*/*cis*) = 45:1. ^{1}H NMR ($CDCl_3$): δ = 7.38–7.24 (m, 7 H), 6.82 (d, 2 H), 4.22–4.18 (m, 3 H), 3.78 (s, 3 H), 3.62 (m, 1 H), 3.31 (m, 1 H), 3.12 (m, 1 H), 1.25 (t, 3 H). ^{13}C NMR ($CHCl_3$): δ = 169.8, 165.0, 156.5, 137.1, 130.9, 128.8, 128.7, 128.6, 127.0, 118.0, 114.4, 61.7, 56.4, 56.3, 55.5, 34.1, 14.0. IR (CH_2Cl_2): 1749, 1745 cm^{-1}.

Ethyl *trans*-1-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidine-2-carboxylate (4c)[19]

Yield: 88%; light-yellow residue; dr (*trans*/*cis*) = 88:1. ^{1}H NMR ($CDCl_3$): δ = 7.38 (m, 4 H), 7.18 (m, 3 H), 6.87 (d, 2 H), 5.38 (d, 1 H), 4.48 (d, 1 H), 4.32 (m, 2 H), 3.81 (s, 3 H), 1.28 (t, 3 H). ^{13}C NMR ($CHCl_3$): δ = 168.5, 161.0, 157.0, 156.9, 130.2, 129.8, 122.9, 118.8, 115.7, 114.5, 83.3, 62.4, 60.2, 55.5, 14.1. IR (CH_2Cl_2): 1752, 1747 cm^{-1}.

Ethyl *trans*-3-(2-Chloroethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (4d)

Yield: 91%; light-yellow residue; dr (*trans*/*cis*) = 86:1. ^{1}H NMR ($CDCl_3$): δ = 7.23 (d, 2 H), 6.87 (d, 2 H), 4.33 (m, 3 H), 3.79 (s, 3 H), 3.77 (t, 2 H), 3.57 (m, 1 H), 2.42 (m, 1 H), 2.23 (m, 1 H), 1.26 (t, 3 H). ^{13}C NMR ($CHCl_3$): δ = 163.6, 160.5, 148.0, 141.4, 123.6, 117.9, 114.5, 114.5, 61.9, 55.5, 14.2. IR (CH_2Cl_2): 1749, 1745 cm^{-1}.

Ethyl *trans*-1-(4-Methoxyphenyl)-3-(methylthiomethyl)-4-oxoazetidine-2-carboxylate (4e)

Yield: 84%; light-yellow residue; dr (*trans*/*cis*) = 38:1. ^{1}H NMR ($CDCl_3$): δ = 7.25 (d, 2 H), 6.89 (d, 2 H), 4.41 (d, 1 H), 4.39 (q, 2 H), 3.82 (s, 3 H), 3.51 (m, 1 H), 3.02 (m, 1 H), 2.97 (m, 1 H), 2.23 (s, 3 H), 1.28 (t, 3 H). ^{13}C NMR ($CHCl_3$): δ = 169.7, 164.0, 156.6, 130.8, 118.0, 114.4, 62.0, 56.4, 55.5, 55.1, 32.0, 16.1, 14.1. IR (CH_2Cl_2): 1750, 1748 cm^{-1}.

Ethyl *trans*-3-Isopropyl-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (4f)[20]

Yield: 81%; light-yellow residue; dr (*trans*/*cis*) = 28:1.

Ethyl *trans*-1-(4-Methoxyphenyl)-3-methyl-4-oxoazetidine-2-carboxylate (4g)[21]

Yield: 71; light-yellow residue; dr (*trans*/*cis*) = 51:1. ^{1}H NMR ($CDCl_3$): δ = 7.26 (d, 2 H), 6.88 (d, 2 H), 4.39 (m, 2 H), 4.31 (d, 1 H), 3.79 (s, 3 H), 3.41 (m, 1 H), 1.51 (d, 3 H), 1.27 (t, 3 H). ^{13}C NMR ($CDCl_3$): δ = 170.0, 168.5, 156.4, 117.9, 114.4, 61.8, 58.6, 55.5, 50.3, 14.2, 13.3. IR (CH_2Cl_2): 1749, 1741 cm^{-1}.

Ethyl *trans*-3-Ethyl-4-oxoazetidine-2-carboxylate (7a)[22]

Yield: 95%; light-yellow residue; dr (*trans*/*cis*) > 99:1.

Acknowledgements

T.L. thanks the NIH (Grant GM064559), the Sloan and Dreyfus Foundations, and Merck & Co. for support. D.H.P thanks Johns Hopkins for a Zeltmann Fellowship.

References and Notes

(1) Current address: Center for Biomedical Research, HIV and AIDS Program, Population Council, 1230 York Avenue, New York, NY 10065, USA.
(2) Current address: National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike Building 8 Rm. 1A-19, Bethesda, MD 20892, USA.
(3) For a review on β-lactam antibiotics, see: (a) Rolinson, G. N. *J. Antimicrob. Chemother.* **1998**, *41*, 589. (b) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publications: New York, **1993**, ; and references therein.
(4) Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1689.
(5) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jih, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365.
(6) For a recent review on β-lactam preparation and significance,see: Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465.
(7) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51.
(8) For catalytic methods of *trans*-β-lactam formation, see: (a) Chen, R.; Yang, B.; Su, W. *Synth. Commun.* **2006**, *36*, 3167. (b) Takahashi, E.; Fujisawa, H.; Yanai, T.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 994. (c) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586. (d) Takahashi, E.; Fujisawa, H.; Yanai, T.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 216. (e) Weatherwax, A.; Abraham, C. J.; Lectka, T. *Org. Lett.* **2005**, *7*, 3461. (f) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537. (g) Tanaka, H.; Hai, A. K. M. A.; Sadakane, M.; Okumoto, H.; Torii, S. *J. Org. Chem.* **1994**, *59*, 3040. (h) Bouthillier, G.; Mastalerz, H.; Menard, M. *Tetrahedron Lett.* **1994**, *35*, 4689. (i) Kita, Y.; Shibata, N.; Tohjo, T.; Yoshida, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1795. (j) Colvin, E. W.;

McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539. (k) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1985**, *14*, 1343.
(9) Kobayashi, S.; Sano, T.; Mukaiyama, T. *Chem. Lett.* **1989**, *18*, 1319.
(10) (a) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 1603. (b) France, S.; Shah, M.; Weatherwax, A.; Wack, H.; Roth, J.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206.
(11) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951.
(12) (a) Hafez, A. M.; Dudding, T.; Wagerle, T. R.; Shah, M. H.; Taggi, A. E.; Lectka, T. *J. Org. Chem.* **2003**, *68*, 5819. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (c) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627. (d) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J. III.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.
(13) Use of the corresponding phosphonium phenoxide provided lower yields and a much slower reaction.
(14) Control experiments whereby a *cis*- or mixed-lactam was mixed with the precatalyst or eventual catalyst or phenoxide showed no hint of epimerization.
(15) We did see the analogous open, silylated product in the *o*-QM cyclization reaction, which subsequently cyclized upon fluoride treatment. See ref. 11 for more information.
(16) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575.
(17) Otera, J.; Fujita, Y.; Fukuzumi, S. *Synlett* **1994**, 213.
(18) (a) Brown, S. J.; Clark, J. H.; Macquarrie, D. J. *J. Chem. Soc., Dalton Trans.* **1988**, 277. (b) Tozawa, T.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 56.
(19) Bose, A. K.; Tsai, M.; Kapur, J. C. *Tetrahedron Lett.* **1974**, *40*, 3547.
(20) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.; Houk, K. N.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2008**, *130*, 875.
(21) Benaglia, M.; Coozi, F.; Puglisi, A. *Eur. J. Org. Chem.* **2007**, *17*, 2865.
(22) Gennari, C.; Schimperna, G.; Venturini, I. *Tetrahedron* **1988**, *44*, 4221.