ORGANIC LETTERS

2012
Vol. 14, No. 7
1784–1787

BINAPHANE-Catalyzed Asymmetric Synthesis of *trans*-β-Lactams from Disubstituted Ketenes and *N*-Tosyl Arylimines

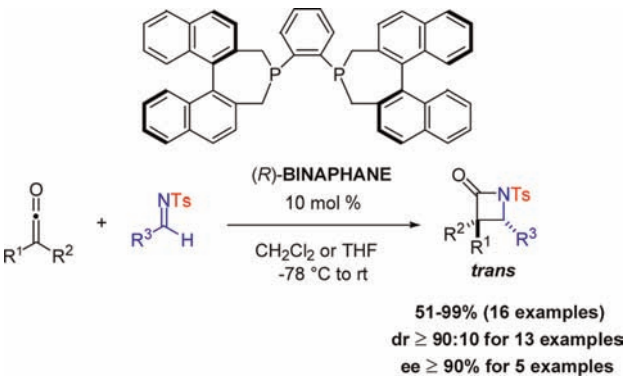
Shi Chen,[†] Eric C. Salo,[†] Kraig A. Wheeler,[‡] and Nessan J. Kerrigan*[,†]

Department of Chemistry, Oakland University, 2200 North Squirrel Road, Rochester, Michigan 48309-4477, United States, and Department of Chemistry, Eastern Illinois University, 600 Lincoln Avenue, Charleston, Illinois 61920-3099, United States

kerrigan@oakland.edu

Received February 15, 2012

ABSTRACT



The development of a BINAPHANE-catalyzed formal [2 + 2]-cycloaddition of disubstituted ketenes and inexpensive *N*-tosyl arylimines that provides access to a variety of highly substituted β-lactams (16 examples) is described. The BINAPHANE catalytic system displays moderate to excellent enantioselectivity (up to 98% ee) and high diastereoselectivity in most cases, favoring formation of the *trans*-diastereomer (13 examples with dr ≥ 90:10).

β-Lactams are molecules that have attracted attention for many years because of their prevalence as key structural features of many antibiotics.[1] They have also been used as intermediates for the synthesis of complex molecules (e.g., taxol).[2] Recently, there has been a demand for access to *trans*-β-lactams due to their potential for use as serine protease inhibitors and β-lactamase inhibitors.[3,4]

An important route to enantioenriched β-lactams relies on the nucleophile-catalyzed formal [2 + 2] cycloaddition of imines and ketenes (often referred to as a Staudinger reaction-like process).[5−8] A few catalytic asymmetric approaches have been reported.[5−10] In 2000, Lectka's groundbreaking work demonstrated that certain alkaloids

[†] Oakland University.
[‡] Eastern Illinois University.

(1) (a) Rolinson, G. N. *J. Antimicrob. Chemother.* **1998**, *41*, 589–603. (b) *Chemistry and Biology of Beta-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vols. 1−3. (c) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publications: New York, 1993.

(2) (a) Kingston, D. G. I. *Chem. Commun.* **2001**, 867–880. (b) Holton, R. A.; Biediger, R. J.; Boatman, P. D. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Boca Raton, FL, 1995; p 97.

(3) (a) Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D.; Alpin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J. *Biochemistry* **1999**, *38*, 7989–7998. (b) Aoyama, Y.; Uenaka, M.; Kii, M.; Tanaka, M.; Konoike, T.; Hayasaki-Kajiwara, Y.; Naya, N.; Nakajima, M. *Bioorg. Med. Chem.* **2001**, *9*, 3065–3075.

(4) (a) Deziel, R.; Malenfant, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1437–1442. (b) Yoakim, C.; Ogilvie, W.; Cameron, D.; Chabot, C.; Grande-Matre, C.; Guse, I.; Hache, B.; Naud, J.; Kawai, S.; O'Meara, J.; Plante, R.; Deziel, R. Antiviral. *Chem. Chemother.* **1998**, *9*, 379–387.

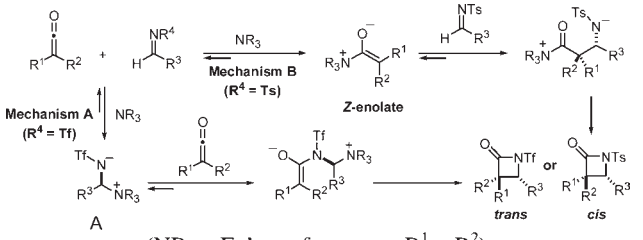
(5) (a) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771–6803. (b) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545–3565. (c) Chen, S.; Salo, E. C.; Kerrigan, N. J. Tertiary amine and phosphine-catalyzed reactions of ketenes and α-halo ketones. In *Science of Synthesis Reference Library, Asymmetric Organocatalysis, Vol. 1, Lewis Base and Acid Catalysts*; List, B., Ed.; Thieme: Stuttgart, 2012; Chapter 1.1.10, pp 455−496.

10.1021/ol3003783
Published on Web 03/12/2012

could catalyze the formal [2 + 2]-cycloaddition of acyl chlorides (precursors to monosubstituted ketenes) with imino esters to give β-lactams with excellent enantioselectivity and good diastereoselectivity favoring the *cis*-isomer.[6] Shortly afterward Fu's group reported that an azaferrocene possessing planar chirality could catalyze the Staudinger reaction of *N*-tosyl imines with disubstituted ketenes (ketoketenes) with high enantioselectivity and good diastereoselectivity favoring the *cis*-isomer.[7] Ye and Smith also showed that chiral NHC catalysts could catalyze the Staudinger reaction of *N*-Boc and *N*-tosyl arylimines with ketoketenes, again favoring formation of the *cis*-diastereomer.[8]

While most of these methods have shown a preference for formation of the *cis*-diastereomer, Fu's group showed that, under chiral azaferrocene catalytic conditions, the use of *N*-triflyl arylimines as coupling partners caused an interesting change in diastereoselectivity to favor the *trans*-diastereomer.[9] Fu's group proposed that the nucleophilic catalyst added first to the highly electrophilic imine to give a zwitterionic species **A** (Scheme 1). Intermediate **A** would then add to the ketoketene before 4-*exo*-*tet* cyclization would give the *trans*-β-lactam and regenerate the catalyst.[9] Lectka's group also reported an anionic 2-aryl-2-imidazoline nucleophilic catalytic system that catalyzed formation of *trans*-β-lactams from imino esters with good to excellent diastereoselectivity.[11]

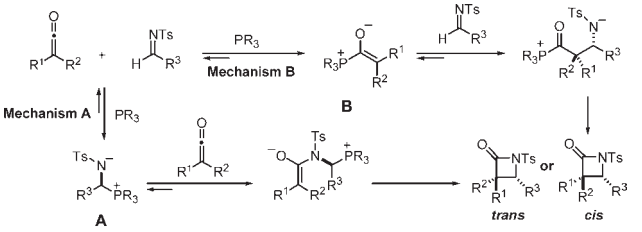
Scheme 1. Fu's Proposed Mechanisms for *trans*-β-Lactam and *cis*-β-Lactam Formation



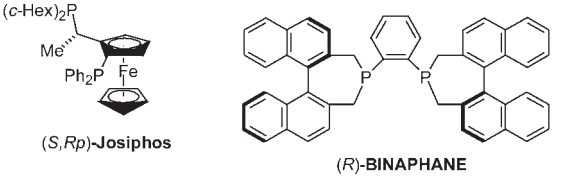
(NR_3 = Fu's azaferrocene; $R^1 > R^2$)

A disadvantage of Fu's elegant asymmetric synthesis of *trans*-β-lactams is that it relies on the use of *N*-triflyl imines which are prepared from the expensive trifluoromethanesulfonamide (ca. \$500/10 g).[12] Moreover, Fu's system works best with alkylarylketenes and diphenylketene as ketene substrates. We considered that the use of *N*-tosyl arylimines as starting materials might provide a more practical approach to *trans*-β-lactams because of the inexpensiveness of the *p*-toluenesulfonamide precursor (ca. \$1/10 g).[12] We reasoned that the use of a chiral phosphine catalyst would favor formation of adduct **A** (rather than **B**) even when a less electrophilic imine such as an *N*-tosyl imine was used (Scheme 2). This would be expected due to the superior nucleophilicity of the phosphine catalyst relative to amine catalysts.[13] Our approach would thus allow *trans*-β-lactams to be accessed from inexpensive *N*-tosyl arylimines.

Scheme 2. Phosphine-Catalyzed Synthesis of *trans*-β-Lactams



(PR_3 = PBu_3 or chiral phosphine; $R^1 > R^2$)



Our studies began with the optimization of the phosphine-catalyzed reaction of ethylphenylketene **1a** with various *N*-tosyl arylimines **2** (Table 1). As with our previous studies on β-lactone forming reactions, BINAPHANE was found to be the optimal catalyst with respect to diastereoselectivity and enantioselectivity, albeit modest (entry 3).[14] A more satisfactory level of enantioselectivity (up to 60% ee) was observed after electronic tuning of the aryl ring of the imine (entry 6). In this case an electron-donating substituent (4-MeO) on the aryl imine led to optimal enantioselectivity. It was found necessary to add a solution of the ketene using a syringe pump to the

(6) (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) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635. (c) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 1603–1605. (d) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206–1215.

(7) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579.

(8) (a) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277–280. (b) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113.

(9) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586–11587.

(10) Huang, Y.; Calter, M. A. *Tetrahedron Lett.* **2007**, *48*, 1657–1659.

(11) Nonenantioselective approaches to *trans*-β-lactams: (a) Weatherwax, A.; Abraham, C. J.; Lectka, T. *Org. Lett.* **2005**, *7*, 3461–3463. (b) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537–2540. (c) Tanaka, H.; Hai, A. K. M. A.; Sadakane, M.; Okumoto, H.; Torii, S. *J. Org. Chem.* **1994**, *59*, 3040–3046.

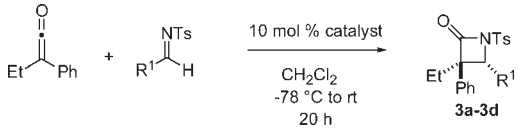
(12) From Aldrich catalog (www.sigmaaldrich.com): *p*-toluenesulfonamide (98%): \$24 for 250 g; trifluoromethanesulfonamide (95%): \$264.50 for 5 g.

(13) (a) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827–1836. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. (c) Wei, Y.; Sastry, G. N.; Zipse, H. *J. Am. Chem. Soc.* **2008**, *130*, 3473–3477.

(14) (a) Mondal, M.; Ibrahim, A. A.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2010**, *12*, 1664–1667. (b) Ibrahim, A. A.; Wei, P.-H.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2010**, *75*, 7901–7904. (c) Ibrahim, A. A.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2009**, *74*, 1777–1780.

solution of phosphine and *N*-tosyl imine over 4 h in order to maximize the yield of β-lactam obtained and minimize competing ketene homodimerization. The success of our approach, from a diastereoselectivity standpoint, seemed to be confirmed by our finding that **3a** (entry 3, Table 1) was obtained with the *trans*-diastereomer as the major isomer (by agreement with Ye's characterization data for **3a**).[8a]

Table 1. Optimization of the Phosphine-Catalyzed Asymmetric Synthesis of β-Lactams



entry	catalyst	R^1	% yield[a]	dr[b]	% ee[c]	product
1	PBu_3	Ph	95	80:20		**3a**
2	Josiphos	Ph	54	72:28	6	**3a**
3	BINAPHANE	Ph	88	92:8	27	**3a**
4	BINAPHANE	4-ClPh	69	85:15	18	**3b**
5	BINAPHANE	4-NO_2Ph	92	88:12	6	**3c**
6	BINAPHANE	4-MeOPh	69	98:2	60	**3d**

[a] % yield is isolated yield for **3**. [b] Diastereomeric ratio (dr) determined by HPLC or ^{1}H NMR analysis of crude. [c] % ee determined by chiral HPLC analysis.

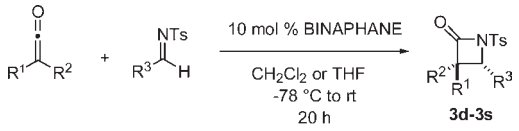
We then proceeded to examine the substrate scope of the reaction with respect to variation of substitution on both the ketene and *N*-tosyl arylimine components (Table 2). Alkylarylketenes were found to be satisfactory substrates with the best results obtained with *n*-butylphenylketene (up to 93% ee, entry 4). However, dialkylketenes were found to be excellent substrates for β-lactam formation, with enantioselectivities up to 98% being observed. This is a particularly significant finding given that Fu's system works best for alkylarylketenes and diphenylketene. As with ethylphenylketene, the enantioselectivity in reactions involving dialkylketenes was found to be highly dependent upon the electronic nature of the imine component (entry 6 vs 9).

Dialkylketenes typically gave a higher enantioselectivity in reactions with *N*-tosyl arylimines possessing an *ortho*-substituent on the aryl ring (entry 8 vs 9), so the steric effect of the substituent appears to be a factor in determining enantioselection as well. In cases that involved the use of excess ketene (e.g., entries 5–11), a ketene dimer was formed as a minor side product but was easily separated from the desired β-lactam by flash column chromatography.

Diastereoselectivity favoring the *trans*-diastereomer was excellent in most cases (≥90:10 for 13 examples). The relative configuration of the major diastereomer was confirmed to be *trans* by X-ray crystallographic analysis of

(15) The relative stereochemistry of β-lactams **3e** and **3t** was determined to be *trans* through single crystal X-ray crystallographic analysis. The relative stereochemistry of most other β-lactams **3a**–**3s** was assigned to be *trans* by analogy.

Table 2. Substrate Scope of the BINAPHANE-Catalyzed Asymmetric Synthesis of β-Lactams



entry	R^1	R^2	R^3	% yield[a]	dr[b]	% ee[c]	product
1	Ph	Me	4-MeOPh	71	95:5	44	**3e**
2	Ph	Et	4-MeOPh	69	98:2	60	**3d**
3	Ph	*n*-Bu	4-MeOPh	57	96:4	52	**3f**
4	Ph	*n*-Bu	Ph	69	92:8	93	**3g**
5[d]	*i*-Pr	Me	2-ClPh	91	87:13	98	**3h**
6	*i*-Pr	Me	4-ClPh	68	94:6	90	**3i**
7[d]	*i*-Pr	Me	4-NO_2Ph	>99	90:10	67	**3j**
8	*i*-Pr	Me	2-FPh	87	99:1	91	**3k**
9	*i*-Pr	Me	4-FPh	81	97:3	70	**3l**
10	*i*-Pr	Me	4-CF_3Ph	90	93:7	73	**3m**
11	*i*-Pr	Me	4-BrPh	93	95:5	85	**3n**
12[d]	*c*-Hex	Me	Ph	56	99:1	65	**3o**
13	*c*-Hex	Me	4-MeOPh	51	92:8	70	**3p**
14	*c*-Hex	Me	2-MePh	69	99:1	91	**3q**
15	Me	Me	2-MeOPh	84	na	82	**3r**
16	Et	Me	2-MeOPh	61	73:27	56	**3s**

[a] % yield is isolated yield for **3**. [b] Diastereomeric ratio (dr) determined by HPLC or ^{1}H NMR analysis of crude. [c] % ee for major diastereomer; determined by chiral HPLC analysis. [d] 15 mol % BINAPHANE was used.

β-lactams **3e** and **3t**, while the absolute configuration of the major diastereomer was determined to be (*R*,*R*) by X-ray crystallographic analysis of **3t** (see Supporting Information for more details).[15,16] In general, good to high enantioselectivity can be obtained for a variety of substitution patterns within both the ketene and imine components, with excellent enantioselectivity (≥90% ee) being obtained for 5 examples.

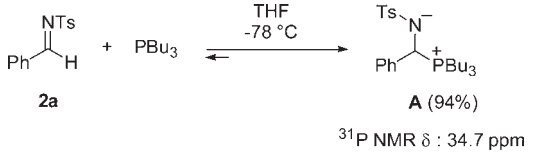
Some support for a mechanism involving initial addition of the phosphine catalyst to the *N*-tosyl arylimine was obtained through ^{31}P NMR spectroscopic studies of the reaction of PBu_3 with *N*-tosyl imine **2a** (Scheme 3). The spectrum of the reaction showed that a significant proportion (>90%) of the phosphorus species was in the form of a tetravalent phosphonium ion, which we tentatively assigned as adduct **A** (Schemes 2 and 3).[17] In contrast, when Fu's group carried out ^{1}H NMR analysis of the reaction of their azaferrocene catalyst with *N*-tosyl imine **2a**, no evidence of an interaction was observed.[9] It is plausible that the divergence in diastereoselectivity of the two methods originates from the two possible modes of addition.

(16) The absolute configuration of β-lactam **3t** was determined to be (*R*,*R*), through single crystal X-ray crystallographic analysis. The absolute stereochemistry of most other β-lactams **3a**–**3s** was assigned to be (*R*,*R*) by analogy.

(17) (a) Zhu, X.-F.; Henry, C. E.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 6722–6723. (b) Hudson, H. R.; Dillon, K. B.; Walker, B. J. ^{31}P NMR Data of Four Coordinate Phosphonium Salts and Betaines. In *Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*; Tebby, J. C., Ed.; CRC Press: Boca Raton, FL, 1991; pp 181–226.

^{31}P NMR monitoring of a PBu_3-catalyzed reaction of *N*-tosyl arylimine **2a** and isopropylmethylketene at −78 °C revealed the presence of a signal for adduct **A** (34.7 ppm), along with a number of other signals in the same region (34−35 ppm). We also analyzed the reaction of PBu_3 with isopropylmethylketene at −78 °C, but no new signal in the 10−40 ppm region was detected, which is where a phosphonium enolate (of type **B**, Scheme 2) would be expected to appear.[18] Therefore, at this point we cannot rule out Mechanism B, involving adduct **B**, and more concrete conclusions regarding the reaction mechanism will await further studies.

Scheme 3. Mechanistic Analysis through ^{31}P NMR Studies



2a **A** (94%)

^{31}P NMR δ : 34.7 ppm

In summary, we have developed a chiral phosphine-catalyzed asymmetric synthesis of β-lactams from inexpensive *N*-tosyl arylimines and a range of disubstituted ketenes, including dialkylketenes. The method affords access to the highly prized *trans*-β-lactams in good to excellent enantioselectivity (7 examples >80% ee, up to 98% ee), and with excellent diastereoselectivity in most cases (dr ≥90:10 for 13 examples). The methodology also tolerates dialkylketenes, substrates which have not been incorporated into the synthesis of enantioenriched *trans*-β-lactams before.[9] Finally, our method nicely complements the *cis*-selective method of Fu's group, whereby use of a different catalyst (azaferrocene or phosphine) in reactions with *N*-tosyl arylimines will provide access to a particular diastereomer of a given β-lactam in a predictable manner.

Acknowledgment. Support has been provided by the National Science Foundation: Grant Nos. CHE-0911483 to N.J.K, CHE-0722547 to K.A.W., CHE-0821487 for NMR facilities at Oakland University, and CHE-1048719 for LC-MS facilities at Oakland University. Support has also been provided by Oakland University (N.J.K.).

Supporting Information Available. Experimental procedures, compound characterization data (PDF) and X-ray crystallographic files (CIF). This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) Wei, P.-H.; Ibrahim, A. A.; Mondal, M.; Nalla, D.; Harzmann, G. D.; Tedeschi, F. A.; Wheeler, K. A.; Kerrigan, N. J. *Tetrahedron Lett.* **2010**, *51*, 6690–6694.