ORGANIC LETTERS

2002
Vol. 4, No. 15
2537−2540

Stereoselective Synthesis of *trans* β-Lactams through Iridium-Catalyzed Reductive Coupling of Imines and Acrylates

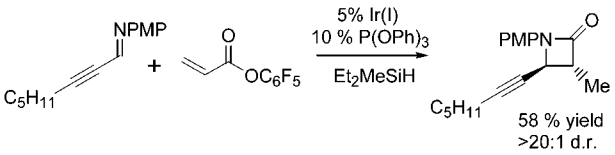
Jennifer A. Townes, Michael A. Evans, Jerome Queffelec, Steven J. Taylor, and James P. Morken*

Department of Chemistry, Venable and Kenan Laboratories, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

morken@unc.edu

Received May 24, 2002

ABSTRACT



Iridium-catalyzed reductive coupling of acrylates and imines provides *trans* β-lactams with high diastereoselection. The optimal catalyst allows for the synthesis of *trans* β-lactams bearing aromatic, alkenyl, and alkynyl side chains. This reaction appears to proceed through a reductive Mannich addition–cyclization mechanism. Examination of substituent effects reveals a linear Hammett correlation for both the N-aryl group on the imine and the aryloxy group on the acrylate, thereby pointing to rate-determining cyclization in the reaction mechanism.

Interest in the stereocontrolled synthesis of β-lacams has been spurred by their use as effective antibiotic agents, protease inhibitors, and cholesterol absorption inhibitors.[1] While a variety of single isomer β-lactams may be accessed by routes such as the Staudinger ketene−imine [2 + 2] cycloaddition[2] and the ester enolate-imine condensation,[3] only three asymmetric catalytic routes to these materials have been described.[4] Alper has reported a rhodium-catalyzed carbonylative ring-opening kinetic resolution of racemic aziridines to provide monosubstituted β-lactams,[5] Lectka has reported a route to *cis* disubstituted β-lactams by amine-catalyzed asymmetric ketene-glyoxal imine cycloaddition,[6a] Doyle and Hashimoto have reported intramolecular C-H insertion reactions,[6b] Fu and Miyaura have reported asymmetric versions of the Kinugasa reaction,[6c] and Tomioka has reported a route to trisubstituted β-lactams by catalytic enantioselective ester enolate-imine condensation.[7] In regards to expanding the scope of catalytic β-lactam synthesis and with pertinence to asymmetric transition-metal catalysis, we disclose a novel and highly diastereoselective iridium-catalyzed synthesis of *trans* β-lactams, which appears to proceed through a reductive Mannich addition−cyclization mechanism.[8,9]

Our studies were initiated by the observation that imine **1**, phenyl acrylate, and Et_2MeSiH could be converted to *trans*

(1) Reviews: (a) *Synthesis of Lactones and Lactams*; Ogliaruso, M. A., Wolfe, J. F., Eds.; John Wiley and Sons: New York, 1993. (b) *The Oranic Chemistry of β-Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993.

(2) Review: Palomo, C.; Aizpura, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235.

(3) Reviews: (a) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563−572. (b) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447−1465.

(4) Review: Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377−4379.

(5) (a) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518. (b) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931.

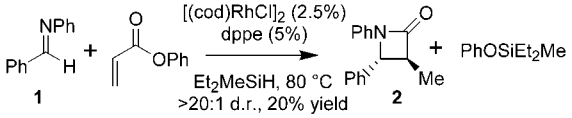
(6) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Youngs, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832. (b) For lead references, see: Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992**, *33*, 7819. Anada, M.; Hashimoto, S.-I. *Tetrahedron Lett.* **1998**, *39*, 9063. (c) Miura, M.; Enna, M.; Okura, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999. Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572.

(7) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715−716.

10.1021/ol020106u CCC: $22.00
Published on Web 06/29/2002

β-lactam **2** and $PhOSiEt_2Me$ under the influence of a catalytic amount of $[(cod)RhCl]_2$ complexed with dppe (Scheme 1).

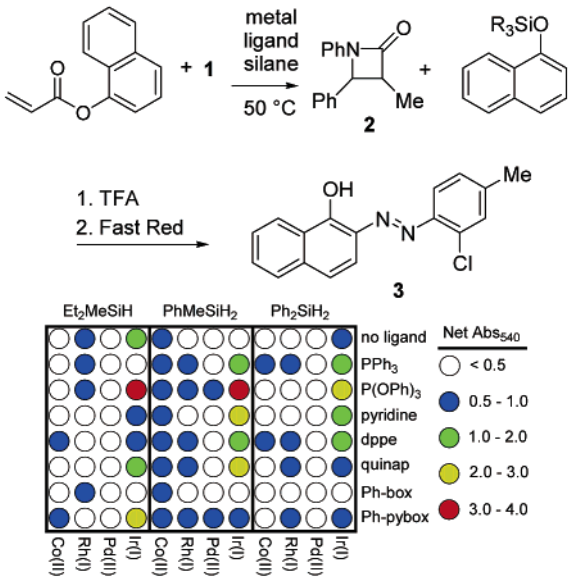
Scheme 1



While this reaction proceeds with good diastereoselectivity (>20:1 *trans*:*cis*), it requires elevated temperatures (80 °C) and provides only modest chemical yield.

In an effort to improve reaction efficiency we examined an array of 96 metal−ligand−silane combinations using a naphthol-based detection assay as described in Scheme 2.[10]

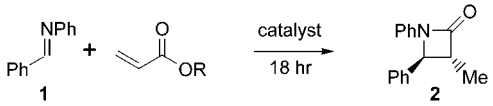
Scheme 2



In each of these experiments, naphthyl acrylate and imine **1** were reacted at 50 °C for 12 h. The reactions were then treated with TFA to hydrolyze the phenolic silyl ether and treated with the diazonium salt Fast Red TR.[11] Parallel measurement of the UV absorbance (540 nm) in each well, before and after addition of Fast Red TR, allowed for detection of diazocoupled 1-naphthol (**3**) produced during the assay sequence (see Scheme 2). The screen was performed twice, each time with a different spatial arrangement of catalysts. Both screens revealed reactivity with a number of iridium salts at 50 °C, whereas the original Rh-dppe complex is ineffective at this temperature as determined from the arrayed assay and also by ^{1}H NMR analysis of isolated experiments. The most effective metal−ligand−silane combination appeared to be $[(cod)IrCl]_2$−$P(OPh)_3$−Et_2MeSiH, which is able to effect transformation at room temperature, converting phenyl acrylate, Et_2MeSiH, and **1** to β-lactam **2** in 13% yield.

To improve product yields and understand the impact of the various reaction components, the series of experiments described in Table 1 was performed. Notably, use of electron-deficient aryl acrylates results in improved product yields with *p*-nitrophenyl acrylate (entry 3) furnishing 56% reaction product and pentafluorophenyl acrylate (entry 4) resulting in a 68% yield of β-lactam at room temperature. The transition metal is required for efficient reaction (entry 6), as is the ligand; reaction without ligand proceeds in only 28% yield (entry 5). Further, a 2:1 ligand:metal complex appears to be optimal for high product yields (cf. entries 4 and 7).

Table 1. Catalytic Reductive Coupling of **1** To Give **2**[a]



entry	R	metal salt	ligand	temp (°C)	yield (%)
1	1-Np	2.5% $[(cod)IrCl]_2$	10% $P(OPh)_3$	50	14
2	Ph	2.5% $[(cod)IrCl]_2$	10% $P(OPh)_3$	25	13
3	pNO_2-Ph	2.5% $[(cod)IrCl]_2$	10% $P(OPh)_3$	25	56
4	C_6F_5	2.5% $[(cod)IrCl]_2$	10% $P(OPh)_3$	25	68
5	C_6F_5	2.5% $[(cod)IrCl]_2$	none	25	28
6	C_6F_5	none	10% $P(OPh)_3$	25	0
7	C_6F_5	2.5% $[(cod)IrCl]_2$	5% $P(OPh)_3$	25	58

[a] Conditions: 1:1:1 ratio of imine/acrylate/silane in dichloroethane solvent. >20:1 *trans*:*cis* stereoisomer ratio obtained in all cases.

Reaction scope was assessed with the series of substrates described in Table 2. In order that reactions reach completion rapidly, all experiments were carried out at 60 °C for 6 h. As noted in entry 1, C-aryl imines furnish acceptable yields of the desired β-lactam in high diastereoselection (determined by ^{1}H NMR analysis). It is also noteworthy that allylic and propargylic imines react without competitive hydrosilation of the C−C π bond. Entries 3−6 demonstrate that a removable *p*-methoxyphenyl group[12] can be used effectively

(8) For related asymmetric reductive aldol reactions, see: (a) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528−4529. (b) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829−1831. For early reports on nonstereoselective reductive aldol reactions, see: (c) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809−4812. (d) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989** 2005−2008. (e) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331−5334. (f) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237−5238.

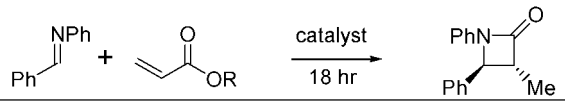
(9) For a review of catalytic enantioselective addition to imines, see: Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.

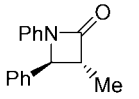
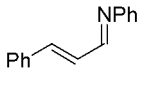
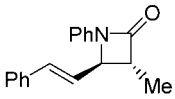
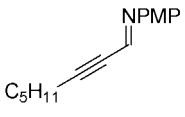
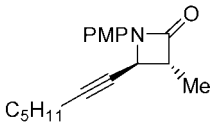
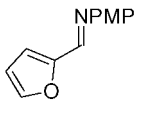
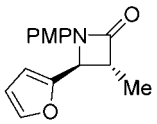
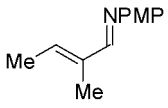
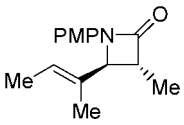
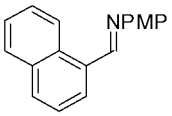
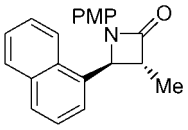
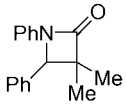
(10) Lavastre, O.; Morken, J. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3163−3165.

(11) Fast Red TR salt (4-chloro-2-methylbenzenediazonium chloride) is commercially available from Aldrich Chemical Co.

(12) The PMP group is readily removed from the β-lactam nitrogen under CAN oxidation conditions, see: (a) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129−1135. (b) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985−7012.

Table 2. Iridium-Catalyzed Synthesis of β-Lactams[a]



entry	imine	product[b]	yield (%)	*trans:cis*[c]
1			68	>20:1
2			70	5.2:1
3			58	>20:1
4			78	>20:1
5			60[d]	>20:1
6			80	>20:1
7			68	NA

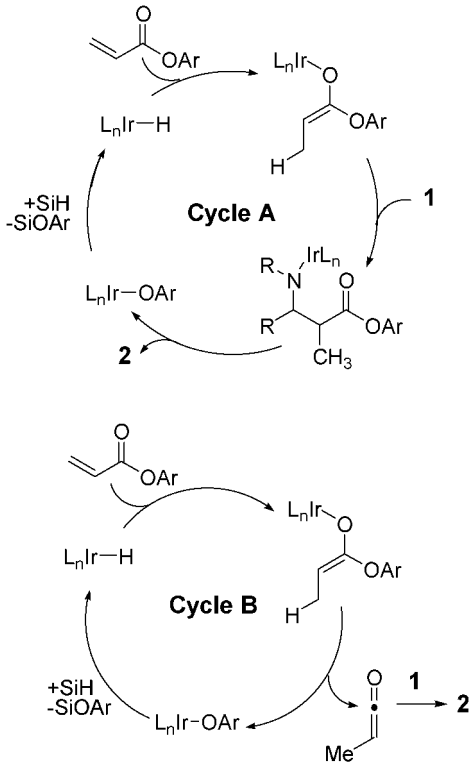
[a] Conditions: 2.5 mol % $[(cod)IrCl]_2$, 10 mol % $P(OPh)_3$, 1.0:2.5:2.5 ratio of imine/pentafluorophenyl acrylate/Et_2MeSiH, 60 °C for 6 h. PMP = *p*-methoxyphenyl. [b] Configuration of product diastereomer determined by analysis of coupling constants and X-ray structure determination (entry 6). [c] Stereochemical ratio determined by ^1H NMR analysis. [d] Could not be freed from ~10% of an impurity.

at the imine nitrogen, and entry 4 indicates that heteroatom functionality does not interfere. While α-substitution on the acrylate is tolerated (entry 7), we have yet to achieve efficient reaction with β substituted acrylates (20% yield, data not shown). We have also been unable to achieve transformation with aliphatic Schiff bases. However, these products should be readily accessible by hydrogenation of the appropriate unsaturated derivative.

In regards to the reaction mechanism, we speculate that an in situ generated iridium hydride reacts with the acrylate to provide an iridium enolate,[13] which then reacts with the imine (**1**) to provide a β-amido ester (cycle A, Scheme 3).[14]

(13) Addition of an Ir(I) hydride to methyl acrylate in the presence of dioxygen is proposed to provide a C-bound iridium enolate. See: Droiun, M.; Harrod, J. F. *Can. J. Chem.* **1985**, *63*, 353−360.

Scheme 3



Subsequent cyclization furnishes the β-lactam and an iridium phenoxide. An alternate mechanism (cycle B, Scheme 3) involving formation of methyl ketene[15] followed by *trans*-selective [2 + 2] cycloaddition[16] is also tenable.[17] We believe cycle A is more likely since it has been reported that methyl ketene (generated by pyrolysis of 2-butanone) reacts with *N*-phenylcinnamaldimine in a 3:1 *trans*:*cis* selectivity at room temperature whereas the corresponding iridium-catalyzed reaction proceeds in >20:1 *trans*:*cis* selectivity at room temperature (59% yield after 48 h using $^iPrMe_2SiH$).[18] Substituent effects at the acrylate aryloxy group and the imine N-aryl group reveal ρ values of 1.28 for the former and −0.48 for the latter (using σ^p) thereby implicating rate-determining cyclization in cycle A (see Supporting Information for these data).

Having established that the stereochemistry-determining step in the iridium-catalyzed reductive coupling of imines

(14) For addition of Pd enolates to imines, see: Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458. Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474−2475.

(15) Lithium enolates of aryl esters eliminate to ketene upon warming to room temperature. See: Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403−5409. The reverse reaction with addition of a Pd-alkoxide to ketene is postulated in a review article. See: Geoffroy, G. L.; Bassner, S. L. In *Advances in Organometallic Chemistry*; Stone, F. G. A., West, R., Eds.; Academic Press: San Diego, 1993; Vol. 28, p 6.

(16) [2 + 2] cycloaddition of imine 1 and methyl ketene is reported to give only the *trans* stereoisomer when the ketene is generated from pyrolysis of 2-butanone. See: Tschamber, T.; Streith, J. *Tetrahedron Lett.* **1980**, *21*, 4503−4506.

(17) [2 + 2] ketene−imine cycloaddition is proposed to proceed through a zwiterionic iminium ion generated by nucleophilic addition of the imine to ketene. For a review, see: ref 1b, pp 295−368.

(18) Streith, J.; Tschamber, T. *Liebigs Ann. Chem.* **1983**, 1393−1408.

and acrylates likely occurs at the transition-metal center, we are now focused on developing asymmetric variants of this catalytic β-lactam synthesis.

Acknowledgment. This work was supported by the NIH (GM 59417-03). J.Q. thanks Elf Aquitaine for a research fellowship. S.J.T. is grateful for an ACS Organic Division fellowship sponsored by Abbott Research Labs. J.P.M. is grateful to Bristol-Myers Squibb, Dow, DuPont, Glaxo-SmithKline, and the David and Lucile Packard Foundation for support.

Supporting Information Available: Characterization data for all new compounds, experimental procedures, tables of crystal data for entry 6, Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020106U