The Journal of
Organic
Chemistry

VOLUME 57, NUMBER 24 NOVEMBER 20, 1992

Communications

Palladium-Catalyzed Regio- and Stereosel ive Allylamination of Allenic Alcohols

Masanari Kimura, Keigo Fugami, Shuji Tanaka, and Yoshinao Tamaru*

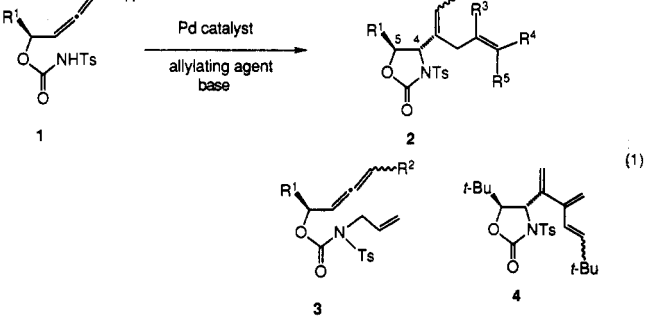
Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, Bunkyo, Nagasaki 852, Japan

Received August 21, 1992

Summary: Palladium [$PdCl_2(PhCN)_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$] catalyzes the reaction of *O*-(2,3-butadienyl) *N*-tosylcarbamates **1** with allylic chlorides to selectively provide *trans*-4,5-disubstituted oxazolidin-2-ones **2** in good yields. Under similar conditions, $Pd(PPh_3)_4$ catalyzes an N-allylation of **1** to give **3**, and chloro-π-allylpalladium(II) dimer promotes a dimerization of **1g** and gives **4** as a major product together with **2**.

Regio- and stereoselective preparation of allylic amines is still a challenge in organic chemistry. In view of the increasing interest in amino sugars[1] and rare amino acids,[2] much effort has been devoted to developing more efficient, stereoselective methods for the synthesis of allylic amines.[3] We recently reported the silver(I)-catalyzed cyclization of *O*-(2,3-butadienyl) *N*-tosylcarbamates **1**,[4] which provided 4-vinyloxazolidin-2-ones, a protected form of 2-amino-3-buten-1-ols, in good yields.[5,6] Unfortunately, this reaction showed only moderate stereoselectivity with respect to the C_4 and C_5 substituents on the oxazolidinone ring.

We now report that palladium catalyzes a similar aminocyclization giving exclusively trans stereoselectivity. Concurrently, allylation takes place at the allenic central carbon to provide allylamination products **2** in good yields (eq 1). The reaction proceeds smoothly at room temperature when a THF solution of **1**, a large excess of an allylic chloride (10–20 equiv),[7] and a catalytic amount of an appropriate palladium species are mixed in the presence of 1 equiv of a base under nitrogen.[8] The use of 1 equiv of an organic or inorganic base is essential to promote the reaction. In the absence of a base, no reaction was discernible. In Table I are summarized the reactions of allyl chloride with various substituted carbamates **1**,[9] and the reactions of a series of allylating agents with *O*-(1-*tert*-



(1)

(1) For reviews, see: (a) Houser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35. (b) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.

(2) (a) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647. (b) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801.

(3) (a) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037. (b) Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486. (c) Jensen, M.; Livinghouse, T. *Ibid.* **1989**, *111*, 4495. (d) Sibi, M. P.; Renhowe, P. A. *Tetrahedron Lett.* **1990**, *31*, 7407. (e) Bernotas, R. C.; Cube, R. V. *Ibid.* **1991**, *32*, 161. (f) Dolle, R. E.; Osifo, K. I.; Li, C.-S. *Ibid.* **1991**, *32*, 5029. (g) Corey, E. J.; Jones, G. B. *Ibid.* **1991**, *32*, 5713. (h) Nayyar, N. K.; Reddy, M. M.; Iqbal, J. *Ibid.* **1991**, *32*, 6965. (i) Magnus, P.; Coldham, I. *J. Am. Chem. Soc.* **1991**, *113*, 672. (j) Grossman, R. B.; Davis, W. N.; Buchwald, S. L. *Ibid.* **1991**, *113*, 2321.

(4) For iodocyclizations of **1** and their transformation to 2-amino-3-buten-1-ols, see: Friesen, R. W.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 4888.

(5) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1991**, *32*, 6359.

(6) For transition-metal-catalyzed cyclizations of allenic amines and alcohols, see: (a) Audin, P.; Doutheau, A.; Gore, J. *Tetrahedron Lett.* **1982**, *23*, 4337. (b) Arseniyadis, S.; Gore, J. *Ibid.* **1983**, *24*, 3997. (c) Walkup, R. D.; Park, G. *Ibid.* **1987**, *28*, 1023. (d) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652.

(7) The reaction of **1a** with 2 equiv of allyl chloride provided **2a** in 32% isolated yield (cf. run 1, Table I). See also footnote 5, Table II.

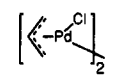
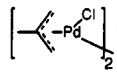
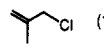
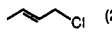
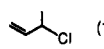
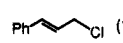
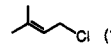
0022-3263/92/1957-6377$03.00/0

Table I. Pd-Catalyzed Allylamination of *O*-(2,3-Butadienyl) *N*-Tosylcarbamates 1 with Allyl Chloride[a]

run	carbamate 1	R^1	R^2	Pd catalyst	base	time (h)	product (% isolated yield)
1	**1a**:	H	H	$PdCl_2(PhCN)_2$	Et_3N	19	**2a** (53)[b]
2	**1b**:	H	Me	$PdCl_2(PhCN)_2$	Et_3N	15	**2b** (63)[c]
3	**1c**:	Me	H	$PdCl_2(PhCN)_2$	Et_3N	17	**2c** (65)
4	**1d**:[d]	Me	Me	$PdCl_2(PhCN)_2$	K_2CO_3	23	**2d** (79)[e]
5	**1e**:	Et	H	$PdCl_2(PhCN)_2$	K_2CO_3	23	**2e** (62)
6	**1f**:	*n*-Pr	H	$PdCl_2(PhCN)_2$	Et_3N	19	**2f** (80)
7	**1g**:	*t*-Bu	H	$PdCl_2(PhCN)_2$	Et_3N	21	**2g** (74)
8	**1g**:	*t*-Bu	H	$Pd_2(dba)_3{\cdot}CHCl_3$[f]	Et_3N	13	**2g** (60)
9	**1g**:	*t*-Bu	H	$Pd(PPh_3)_4$[f]	Et_3N	17	**3g** (89)

[a] A THF solution of 1 (1 mmol), Pd catalyst (0.1 mmol), base (1.0 mmol), and allyl chloride (20 mmol) was stirred at rt under N_2. For **2a–g**, $R^3 = R^4 = R^5 = H$. [b] In addition to **2a**, 4-vinyloxazolidin-2-one was obtained in 8% yield. [c] A mixture of (*E*)- and (*Z*)-**2b** (2.3:1) was obtained. [d] A diastereomeric mixture of **1d** (1:1.4) was used. [e] A chromatographically inseparable mixture of **2d** (ca. 1:2:11:14) was obtained. The stereochemistry of the components was not determined. [f] In this run, a smaller amount of palladium (0.05 mmol) was applied.

Table II. Allylamination of 1g with Various Allylating Agents[a]

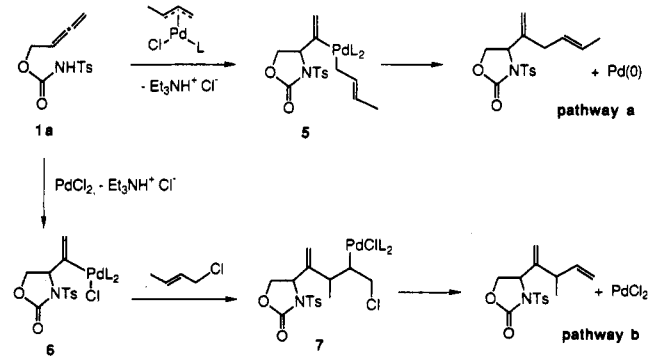
run	allylating agent (equiv)	time (h)	product[b] (% isolated yield)
1[c]	 (1)	42	**2g** (17), **4** (50)[d]
2[c]	 (1)	40	**2h** (5), **4** (31)[d]
3	 (10)	23	**2h** (46)
4	 (20)[e]	8	**2i** (76)
5	 (10)	15	**2i** (78)
6	 (10)	11	**2j** (60)
7	 (10)	8	**2k** (51)

[a] A mixture of **1g**, $PdCl_2(PhCN)_2$ (0.1 equiv), allylating agent, and triethylamine (1.0 equiv) in dry THF (3 mL/mmol of **1d**) was stirred at rt under N_2. [b] **2h** (R^1 = *t*-Bu, R^2 = H, R^3 = Me, $R^4 = R^5$ = H); **2i** (R^1 = *t*-Bu, $R^2 = R^3$ = H, R^4 = Me, R^5 = H); **2j** (R^1 = *t*-Bu, $R^2 = R^3$ = H, R^4 = Ph, R^5 = H), **2k** (R^1 = *t*-Bu, $R^2 = R^3$ = H, $R^4 = R^5$ = Me). [c] The reaction was carried out in the absence of $PdCl_2(PhCN)_2$. [d] A mixture of (*E*)- and (*Z*)-**4** (2.2:1) was obtained. [e] With 2 equiv of crotyl chloride, the same product was obtained in 65% yield.

butyl-2,3-butadienyl) *N*-tosylcarbamate (**1g**) are summarized in Table II.

$PdCl_2(PhCN)_2$ was most often utilized as the palladium catalyst. $Pd_2(dba)_3{\cdot}CHCl_3$ was also used (run 8, Table I).

Scheme I. Reaction Pathways for the Pd-Catalyzed Allylamination of 1a with Crotyl Chloride



However, it turned out that $Pd(PPh_3)_4$, one of the most popular Pd(0) catalysts, catalyzed a completely different reaction (run 9); an allylation of **1** at the nitrogen atom[10] took place exclusively and furnished **3** in high yield.

The scope and utility of the present reaction for preparation of dienylamino alcohols is apparent from the examination of Tables I and II, which reveal the wide structural flexibility in both **1** and the allylating agents, respectively. The high regio- and stereoselectivity should also be noted. Except for **2d**,[11] trans-4,5-disubstituted oxazolidin-2-ones **2** were obtained exclusively, irrespective of the steric bulk of the R^1 substituents. However, changing the R^2 substituents resulted in the formation of a mixture of stereoisomers of **2** (runs 2 and 4, Table I).

The reaction pathway is more complicated than it first appears. In Scheme I are illustrated two pathways, using **1a** and crotyl chloride as representative reactants, that merit consideration.[12] Pathway a starts with a cycloaminopalladation of **1a** with π-allylpalladium(II) to give vinylcrotylpalladium(II) intermediate **5**.[13] Pathway b is

(8) Typical procedure (run 3, Table I): To a mixture of $PdCl_2(PhCN)_2$ (38.4 mg, 0.1 mmol) and *O*-(1-methyl-2,3-butadienyl) *N*-tosylcarbamate (**1c**, 281 mg, 1 mmol) was added 3 mL of dry THF via syringe under N_2. To the resulting homogeneous solution were successively added allyl chloride (1.6 mL, 20 mmol) and triethylamine (0.15 mL, 1 mmol). After being stirred for 17 h at rt, the mixture was diluted with EtOAc and washed with saturated $NaHCO_3$. After the EtOAc solution was dried over $MgSO_4$, evaporation of the volatile organics gave a sticky oil, which was chromatographed on silica gel. Elution with benzene gave 209 mg (65%) of **2c** as a colorless oil: IR (neat film) 1785 (s), 1370 (s), 1170 (s), 950 (s), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (d, J = 6.2 Hz, 3 H), 2.45 (s, 3 H), 2.60 (dd, J = 7.0, 16.5 Hz, 1 H), 2.69 (dd, J = 7.0, 16.5 Hz, 1 H), 4.33 (dq, J = 3.3, 6.2 Hz, 1 H), 4.45 (d, J = 3.3 Hz, 1 H), 5.03 (ddd, J = 1.5, 2.9, 17.2 Hz, 1 H), 5.07 (t, J = 1.5 Hz, 1 H), 5.11 (ddd, J = 1.5, 2.9, 10.3 Hz, 1 H), 5.15 (s, 1 H), 5.69 (ddt, J = 10.3, 17.2, 7.2 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.93 (d, J = 8.4 Hz, 2 H); HRMS calcd for $C_{16}H_{19}NO_4S$ (M^+) 321.1035, found 321.1038.

(9) For preparation of allenyl alcohols, see: Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 720.

(10) (a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (b) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99. (c) Tamaru, Y.; Bando, T.; Kawamura, Y.; Okamura, K.; Yoshida, Z.; Shiro, M. *J. Chem. Soc., Chem. Commun.*, in press.

(11) Detection of a pair of four methyl doublets (ca. 1:2:11:14) in the 400-MHz ^1H NMR spectrum of **2d** suggests the formation of the *cis* isomers with respect to the C_4 and C_5 substituents (run 4, Table I).

(12) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.

(13) Alternatively, π-allylpalladium(II) may add to the allenic double bond of **1a** to form a 2-allyl-π-allylpalladium(II) intermediate, which may undergo a nucleophilic ring closure to give **2**. For intramolecular additions of π-allylpalladium compounds to double bonds, see: Yoo, S.-E.; Lee, S.-H.; Yi, K.-Y.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 6877. For the Pd-catalyzed 1,2-addition to allenes, see: (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. (b) Koerber, K.; Gore, J.; Vatele, J.-M. *Tetrahedron Lett.* **1991**, *32*, 1187. (c) Ganthier, V.; Cazes, B.; Gore, J. *Ibid.* **1991**, *32*, 915. (d) Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615. See also ref 6d.

initiated by a cycloaminopalladation of **1a** with $PdCl_2$ to form vinylpalladium(II) chloride intermediate **6**, which adds to the double bond of crotyl chloride in such a way as to give β-chloroethylpalladium(II) chloride intermediate **7**.[14] Reductive elimination of a Pd(0) species from **5** or dechloropalladation from **7** provides the final product.

Of these possibilities, pathway b may be safely excluded because it predicts the wrong regiochemistry for the methyl substituent in the product of the reaction of **1** and crotyl chloride (run 4, Table II). Pathway b would be acceptable if crotyl chloride isomerizes to α-methallyl chloride under the reaction conditions and **6** reacted only with α-methallyl chloride. However, no such isomerization was detected when the reaction was monitored by VPC. Pathway a seems to be flawed by the slow reactions and the low yields of **2** observed for the reactions of **1** with stoichiometric amounts of chloro-π-allylpalladium(II) dimers (runs 1 and 2, Table II). In these reactions, to our surprise, nonallylated product **4**, a formal dimerization product of **1g**, was obtained as a major product.[15]

Thus, neither of the mechanisms shown in Scheme I seems to be satisfactory. Nevertheless, we believe that the π-allylpalladium route (pathway a) is the most probable. The side reactions caused by some π-allylpalladium species, which furnish either **3** (run 9, Table I) or **4** (runs 1 and 2, Table II), could be attributed to subtle differences in the ligands on palladium or to the form in which the palladium species exist in solution.

Work is in progress to optimize the yield, to clarify the mechanism, and to apply our route to the synthesis of physiologically important natural and synthetic products.

Acknowledgment. This work was supported by Grants from the Ministry of Education, Science and Culture, Japanese Government (No. 04453089 and No. 04217228) and the CIBA-GEIGY Foundation.

Supplementary Material Available: Characterization data and ^1H NMR spectra for **2–4** (31 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816.

(15) Satisfactory spectral (IR, ^1H NMR) and analytical data (HRMS) were obtained for **2–4**.

A Convenient Procedure for the Synthesis of Bis-steroidal Pyrazines: Models for the Cephalostatins

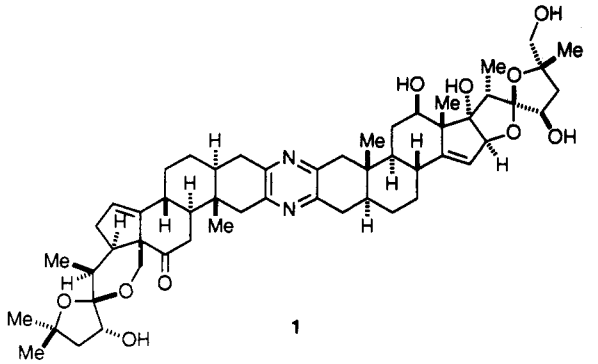
Stephen C. Smith and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

Received September 10, 1992

Summary: Efficient routes have been developed for both symmetrical and unsymmetrical bis-steroidal pyrazines from readily available precursors.

The cephalostatins are a group of complex steroidal pyrazine alkaloids that were isolated from the marine worm *Cephalodiscus gilchristi*.[1] They are powerful cytotoxins against the PS cell line (ED_{50} 10^{-7}–10^{-9} μg/mL) and therefore have potential applications as antitumor agents. However, they are rare marine natural products and are available in only small amounts. For example, 166 kg of *C. gilchiristi* (5-mm long tube worms), provided only 139 mg of cephalostatin 1 (**1**) and a total of 272 mg of other cephalostatins. Although the cephalostatins are among the most potent cytotoxins ever screened by National Cancer Institute in the PS system, the limited availability of the natural materials has limited in vivo tests.[2] Because of this limited availability, we have embarked on a program of total synthesis of the cephalostatins. In this paper, we report three new procedures for the formation of bis-steroidal pyrazines. Two of these procedures are applicable to the high-yield preparation of symmetrical bis-steroidal pyrazines, and the other is useful for the synthesis of unsymmetrical analogs, which were hitherto unknown except as embodied in the cephalostatins themselves.



1

A convenient method for the preparation of symmetrical bis-steroidal pyrazines is summarized in Scheme I. Bromination of 3-cholestanone (**2**) at the 2-position,[3] followed by displacement of bromide with sodium azide,[4] provided azido ketone **3** in about 50% overall yield. Treatment of **3** with triphenylphosphine in aqueous THF gave a crude product which was treated with *p*-toluenesulfonic acid in ethanol to obtain pyrazine **4** in 87% yield. We believe that compound **4** results from dimerization of the α-amino ketone that is formed by the Ph_3P-mediated reduction of the azido group. Previously, symmetrical bis-steroidal

(1) (a) Pettit, G. R.; Kamano, Y.; Dufresne, C.; Inoue, M.; Christie, N.; Schmidt, J. M.; Doubek, D. L. *Can. J. Chem.* **1989**, *67*, 1509. (b) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006. (c) Pettit, G. R.; Inoue, M.; Kamano, Y.; Dufresne, C.; Christie, N. D.; Niven, M. L.; Herald, D. L. *J. Chem. Soc., Chem. Commun.* **1988**, 865. (d) Pettit, G. R.; Kamano, Y.; Inoue, M.; Dufresne, C.; Boyd, R.; Herald, D. L.; Schmidt, J. M.; Doubek, D. L.; Christie, N. D. *J. Org. Chem.* **1992**, *57*, 429.

(2) Dr. Matthew Suffness, National Cancer Institute, personal communication.

(3) Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 417.

(4) Schönecker, V. B.; Ponsold, K. *J. Für. Prakt. Chem. Bond.* **1971**, *313*, 817.

0022-3263/92/1957-6379$03.00/0