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Diastereoselective Synthesis of Hexahydro-3*H*-pyrrolyzin-3-ones through Pd-Catalyzed Carboamination

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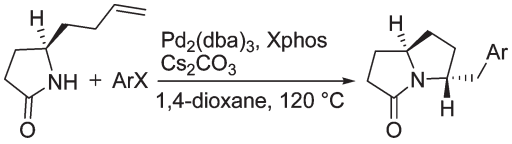
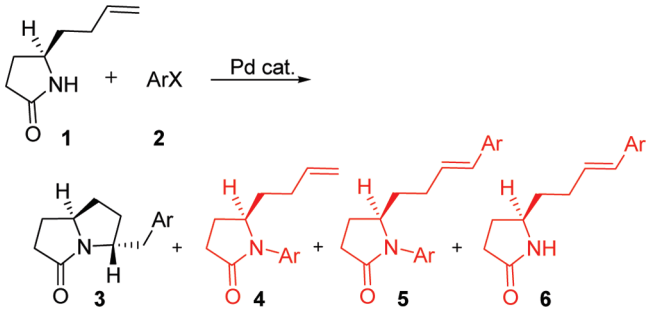


The reaction of readily available (5*R*)-5-but-3-en-1-ylpyrrolidin-2-one with aryl bromides, chlorides, or triflates in the presence of $Pd_2(dba)_3$, Xphos, and Cs_2CO_3 in 1,4-dioxane at 120 °C affords (5*R*,7a*R*)-5-aryl hexahydropyrrolizidin-3-ones in good to high yields through a diastereoselective carboamination reaction. Aryl iodides are less successful substrates than bromides and chlorides.

The hexahydropyrrolizine motif is abundant in many biologically active compounds.[1] For example, hexahydropyrrolizine derivatives have been shown to possess interesting properties as glycosidase inhibitors,[2] nonopiate antinociceptive agents,[3] histaminic H1 and H3 antagonists,[4] and antibacterial agents.[5] Because of this, several synthetic approaches to the preparation of this class of compounds have been described in the literature.[2c,d,6] However, although palladium catalysis proved to be a powerful and versatile tool for the construction of heterocyclic rings, no examples of construction of the hexahydropyrrolidizinone system through palladium-catalyzed synthesis have been reported.

Herein we report that (5*R*,7a*R*)-5-aryl hexahydropyrrolizidin-3-ones **3** can be prepared through a diastereoselective palladium-catalyzed carboamination of (5*R*)-5-but-3-en-1-ylpyrrolidin-2-one **1** with aryl halides (Scheme 1).

SCHEME 1. Synthesis of (5*R*,7a*R*)-5-Aryl Hexahydropyrrolizidin-3-ones 3 from (5*R*)-5-But-3-en-1-ylpyrrolidin-2-one 1 and Aryl Halides



Compound **1** was readily prepared as described previously[7] from the commercially available (5*R*)-5-(hydroxymethyl)pyrrolidin-2-one through its conversion into the corresponding tosyl derivative followed by a nucleophilic substitution step with allylmagnesium bromide.

We initiated our study by examining the influence of ligands, bases, and solvents for the reaction of **1** with 4-bromobiphenyl **2a** in the presence of 2.5 mol % of $Pd_2(dba)_3$ at 120 °C. The results of the optimization studies are summarized in Table 1. After an initial screen of ligands (Xantphos, Xphos, Sphos;[8] 0.05 equiv), bases (NaOBu-*t*, Cs_2CO_3; 1.5 equiv), and solvents (toluene, 1,4-dioxane; 4 mL)

(1) For recent reviews, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (b) Watson, A. A.; Fleet, G: W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

(2) For selected references, see: (a) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron Asymmetry* **2000**, *11*, 1. (b) Yamashita, T; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. J. *Nat. Prod.* **2002**, *65*, 1875. (c) Kato, A.; Kano, E.; Adachi, I.; Molyneux, R. J.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Wormald, M. R.; Kizu, H.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 325. (d) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315. (e) Cicchi, S.; Marradi, M.; Vogel, P.; Goti, A. *J. Org. Chem.* **2006**, *71*, 1614.

(3) Carson, J. R.; Carmosin, R. J.; Vaught, J. L.; Gardocki, J. F.; Costanzo, M. J.; Raffa, R. B.; Almond, H. R. *J. Med. Chem.* **1992**, *35*, 2855.

(4) Apodaca, R.; Carruthers, N. I.; Carson, J. R.; Chai, W.; Kwok, A. K.; Li, X.; Lovenberg, T. W.; Rudolph, D. A.; Shah, C. R. WO 2001-US29624 20010921; *Chem. Abstr.* **2001**, *136*, 263105.

(5) Nash, R. J.; Wolferstan, P.; Fleet, G. W. J.; Van Ameijde, J.; Horne, G. WO 2004-GB4624 20041103; *Chem. Abstr.* **2004**, *142*, 487686.

(6) (a) Holmes, A. B.; Smith, A. L.; Williams, S. F. *J. Org. Chem.* **1991**, *56*, 1393. (b) Murray, A.; Proctor, G. R. *Tetrahedron Lett.* **1995**, *36*, 291. (c) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802. (d) Bowman, W. R.; Broadhurst, M. J.; Coghlan, D. R.; Lewis, K. A. *Tetrahedron Lett.* **1997**, *38*, 6301. (e) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621. (f) Coldham, J.; Hufton, R.; Price, K. N.; Rathmell, R. E.; Snowden, D. J.; Vennal, G. P. *Synthesis* **2001**, 1523. (g) Roche, C.; Kadlecikovà, K.; Veyron, A.; Delair, P.; Philouze, C.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 8352. (h) Smith, A. B. III; Kim, D. S. *J. Org. Chem.* **2006**, *71*, 2547. (i) Quiroz, T.; Corona, D.; Covarruvias, A.; Avila-Zarraga, J. G.; Romero-Ortega, M. *Tetrahedron Lett.* **2007**, *48*, 1571 and references cited therein. (j) Quinet, C.; Jourdain, P.; Hermans, C.; Ates, A.; Lucas, I.; Markò, I. E. *Tetrahedron* **2008**, *64*, 1077. (k) Quinet, C.; Ates, A.; Markò, I. E. *Tetrahedron Lett.* **2008**, *49*, 5032. (l) Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615. (m) Zimmer, R.; Collas, M.; Czerwonka, R.; Hain, U.; Reissig, H.-U. *Synthesis* **2008**, 237.

(7) Compound **1** has been converted into an approximately 70:30 diastereoisomeric separable mixture of 5-[(phenylseleno)methyl]hexahydro-3*H*-pyrrolizin-3-ones through 5-*exo*-*trig* electrophilic selenocyclization with *N*-(phenylseleno)phthalimide: (a) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Scarponi, C. *Tetrahedron: Asymmetry* **2008**, *19*, 2411. See also: (b) Occhiato, E. G.; Brandi, C.; Ferrari, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542.

(8) Davephos = 2-(2′-*N*,*N*-dimethylaminobiphenyl)dicyclohexylphosphine; Sphos = 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine; Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene; Xphos = 2-(2′,4′,6′-triisopropylbiphenyl)dicyclohexylphosphine.

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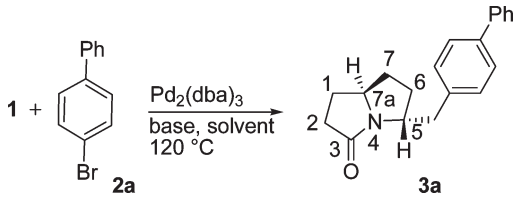
TABLE 1. Optimization Studies[a]



entry	ligand	base	solvent	time (h)	yield (%) of **3a**
1	Xantphos	NaOBu-*t*	toluene	24	
2	Xphos	NaOBu-*t*	toluene	21	34
3	Xphos	Cs_2CO_3	1,4-dioxane	24	34
4	Sphos	NaOBu-*t*	1,4-dioxane	21	24
5	Xphos	Cs_2CO_3	1,4-dioxane	8	55[b]
6	Xphos	Cs_2CO_3	1,4-dioxane	8	53[c]
7	Xphos	Cs_2CO_3	toluene	6	34[c]
8	Xphos	K_3PO_4	1,4-dioxane	21	53[c]
9	Davephos	Cs_2CO_3	1,4-dioxane	20	23[c]
10	Xphos	Cs_2CO_3	1,4-dioxane	4	60[c,d]
12	Xphos	K_3PO_4	1,4-dioxane	22	51[c,d]
13	Xphos	Cs_2CO_3	1,4-dioxane	3	65[b,d]

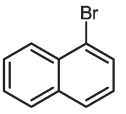
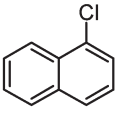
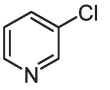
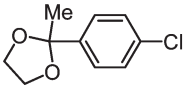
[a]Unless otherwise stated, reactions were carried out at 120 °C in a 0.075 M solution, under an argon atmosphere, using 1 equiv of **2a**, 1.5 equiv of **1**, 1.2 equiv of base, 0.025 equiv of $Pd_2(dba)_3$, 0.05 equiv of ligand. [b]In a 0.03 M solution. [c]In a 0.02 M solution. [d]With 0.1 equiv of Xphos.

(Table 1, entries 1−4), we found that the use of Xphos and Cs_2CO_3, in 10 mL of 1,4-dioxane produced **3a** diastereoselectively after 8 h in 55% yield (Table 1, entry 5). Further dilution of the reaction mixture (15 mL) did not give better results (Table 1, entries 6−9), whereas an increase of the Xphos to Pd ratio (2:1) enhanced the yield of **3a** to 60% (Table 1, entry 10). The best result (65% yield) was obtained by using 0.1 equiv of Xphos in 10 mL of 1,4-dioxane (Table 1, entry 13). The main side products observed were **4a** and **5a** (Ar = 4-PhC_6H_4).

The cis fusion of the bicyclic system was established on the basis of the chemical shift values of the proton and the carbon-13 at the 7a position[7,9] and the relative configuration of the C(5) was assigned by NOESY experiments.[10] The configuration of the C(7a) was stable under reaction conditions. This was established by HPLC analysis on a chiral column Chiracel OD-H, which showed that **3c**, the product obtained via the reaction of 4-chloroanisole with (5*R*)-5-but-3-en-1-ylpyrrolidin-2-one (76% yield, see Table 2, entry 7), is enantiomerically pure and that the reaction of 4-chloroanisole with (5*S*)-5-but-3-en-1-ylpyrrolidin-2-one *ent*-**1** affords stereoselectively *ent*-**3c** (75% yield). Combining these data, we assigned the (5*R*,7a*R*) configuration to the stereogenic centers of **3a** and **3c**. The stereochemistry of all the other 5-aryl hexahydropyrrolizidin-3-ones prepared (vide infra) has been assigned on the basis of these data.

Using the optimized conditions, we next explored the scope and generality of the process (Table 2). Clean formation of 5-aryl hexahydropyrrolizidin-3-ones **3** was observed with a variety of aryl and heteroaryl bromides, chlorides, and triflates. The reaction tolerates a variety of substituents including aldehyde, ketone, ether, ester, and nitro groups. Aryl iodides are less successful substrates than bromides and chlorides (Table 2, compare entry 6 with entries 4 and 5). Aryl iodides are more prone to give free NH vinylic

TABLE 2. Synthesis of 5-Aryl Hexahydropyrrolizidin-3-ones 3[a]

entry	aryl halide **2**	time (h)	yield % of **3**	
1	4-PhC_6H_4-Br	3	65	**3a**
2	4-PhC_6H_4-Cl	7	70	**3a**
3	4-PhC_6H_4-OTf	5	63	**3a**
4	3-$MeOC_6H_4Cl$	24	76	**3b**[b]
5	3-$MeOC_6H_4Br$	20	62	**3b**[c]
6	3-$MeOC_6H_4I$	6	48	**3b**[d]
7	4-$MeOC_6H_4Cl$	24	76	**3c**
8	3-$CF_3C_6H_4Br$	24	74	**3d**
9	3-$CF_3C_6H_4Cl$	21	72	**3d**
10	4-MeC_6H_4Cl	24	71	**3e**
11	2-MeC_6H_4Cl	22	41	**3f**[e]
12	3-$MeOCOC_6H_4Cl$	21	85	**3g**
13	4-$PhCOC_6H_4Cl$	21	85	**3h**
14	3-$CHOC_6H_4Br$	6	68	**3i**
15	3-FC_6H_4Br	24	78	**3j**
16	2-$NO_2C_6H_4Cl$	24	49	**3k**
17		24	70	**3l**
18		24	68	**3l**
19		24	90	**3m**
20		24	80	**3n**

[a]Reactions were carried out at 120 °C in 10 mL of 1,4-dioxane, under an argon atmosphere, in a 0.03 M solution, using 1 equiv of **2**, 1.2 equiv of **1**, 1.5 equiv of Cs_2CO_3, 0.025 equiv of $Pd_2(dba)_3$, 0.1 equiv of Xphos. [b]**6b** was isolated in 10% yield. [c]**6b** was isolated in 15% yield. [d]**6b** was isolated in 45% yield. [e]**6f** (Ar = 2-MeC_6H_4) was isolated in 40% yield.

substitution derivatives as shown by the increase of the yield of **6b** (Ar = 3-$MeOC_6H_4$) on going from 3-chloroanisole (10% yield) to 3-bromoanisole (15% yield) to 3-iodoanisole (45% yield) (Table 2, entries 4−6). Only with ortho-substituted aryl halides were the corresponding hexahydropyrrolizidin-3-ones isolated in moderate yields (Table 2, entries 11 and 16), most probably because of steric effects.

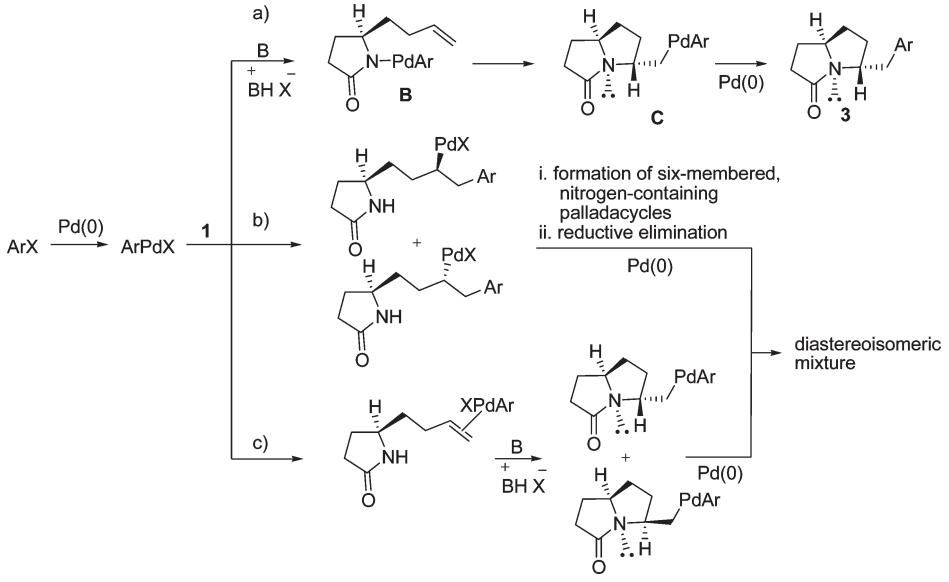
The mechanism of this reaction is most probably analogous to that previously described for related palladium-catalyzed carboaminations of alkenes[11] (Scheme 2, path a;

(9) Jones, T. H.; Blum, M. S. *J. Org. Chem.* **1980**, *45*, 4778 and references cited therein.

(10) See the Supporting Information for further details.

(11) (a) For a recent review, see: Wolfe, J. P *Synlett* **2008**, 2913. See also: (b) Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907. (c) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533. (d) Nakhla, J. S.; Schultz, D. M.; Wolfe, J. P. *Tetrahedron* **2009**, *65*, 6549. (e) Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107.

SCHEME 2. Proposed Mechanism for the Synthesis of (5*R*,7a*R*)-5-Aryl Hexahydropyrrolizidin-3-ones 3



ligands are omitted for clarity). The nitrogen displacement of the halide in the arylpalladium complex **A** affords the amido palladium adduct **B** that undergoes an intramolecular *syn* aminopalladation to give the intermediate **C**. A subsequent reductive elimination affords the desired (5*R*,7a*R*)-5-aryl hexahydropyrrolizidin-3-one **3** and regenerates the active palladium species.

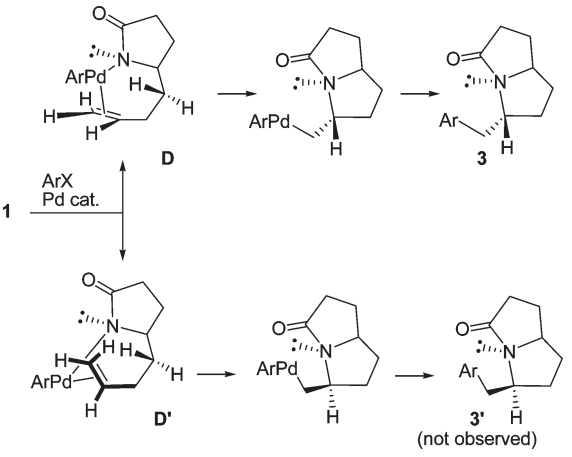
The alternative mechanism involving an initial carbopalladation step, followed by the formation of a six-membered ring, nitrogen-containing palladacycle (via an intramolecular nucleophilic attack of the nitrogen atom to palladium) and reductive elimination (Scheme 2, path b), appears less likely due to the high stereoselectivity for the formation of products. If the reactions were to occur through the formation of carbopalladation adducts, it is likely that a diastereoisomeric mixture of 5-aryl hexahydropyrrolizidin-3-ones would be observed. Similar considerations (i.e., formation of a diastereoisomeric mixture) apply to the mechanism involving an intramolecular nucleophilic attack of the nitrogen on the olefinic moiety activated by a σ-arylpalladium complex generated in situ[12] (Scheme 2, path c).

To explain the diastereoselectivity of the reaction, we suggest that the stereochemistry-determining step is the insertion of the alkene into the Pd−N bond of the conformer **D**. As shown in Scheme 3, the conversion of **1** to the diastereoisomeric derivative **3′** would proceed via the conformer **D′**. The presence of repulsive nonbonding interaction between one of the external olefinic protons and one of the C(1) hydrogens would disfavor the reaction via this conformer.

In conclusion, we have shown that palladium catalysis provides an efficient tool for the construction of the hexahydropyrrolizine motif. The new method allows the preparation of (5*R*,7a*R*)-5-aryl hexahydropyrrolizidin-3-ones in good to high yields from readily available (5*R*)-5-but-3-en-1-ylpyrrolidin-2-one and aryl bromides, chlorides, or triflates through a diastereoselective carboamination process. A halide effect on the reaction outcome has been observed.

(12) For a seminal example of this chemistry, see: Fournet, G.; Balme, G.; Gore, J. *Tetrahedron Lett.* **1989**, *30*, 69.

SCHEME 3. Proposed Stereochemical Pathway for the Formation of (5*R*,7a*R*)-5-Aryl Hexahydropyrrolizidin-3-ones 3



Aryl iodides have been found to be less successful substrates than bromides and chlorides.

Experimental Section

General Procedure. (5*R*,7a*R*)-5-(4-Phenylbenzyl)hexahydropyrrolizidin-3-one (3a). $Pd_2(dba)_3$ (0.0069 g, 0.0075 mmol), XPhos (0.0142 g, 0.015 mmol), 4-bromobiphenyl (0.070 g, 0.30 mmol), and Cs_2CO_3 (0.1589 g, 0.45 mmol) were stirred in dry 1,4-dioxane (10 mL) at room temperature for 30 min, and then (*R*)-5-(but-3-enyl)pyrrolidin-2-one (0.050 g, 0.360 mmol) dissolved in 5 mL of 1,4-dioxane was added. The resulting mixture was stirred at 120 °C for 3 h. After this time, the mixture was concentrated under reduced pressure and the residue was purified by chromatography (silica gel, 35 g; 20/80 v/v *n*-hexane/EtOAc) to give 0.056 g (65% yield) of **3a**: mp 118−119 °C; $[\alpha]_D$ = +117.7 (*c* = 1.10, $CHCl_3$); IR (KBr) 2936, 1675, 1407, 807 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (d, *J* = 7.6, 2H Hz), 7.55 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.30−7.25 (m, 2H), 4.22−4.11 (m, 1H), 3.82−3.72 (m, 1H), 3.14 (dd, J_1 = 4.0 Hz, J_2 = 16.0 Hz, 1H), 2.83 (dd, J_1 = 4.0 Hz, J_2 = 16.0 Hz, 1H), 2.82−2.74 (m, 1H), 2.47 (ddd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, J_3 = 16.0, 1H), 2.31−2.21 (m, 1H), 2.21−2.11 (m, 1H), 2.11−1.63

(m, 3H), 1.35−1.21 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 175.0, 140.9, 139.2, 138.0, 130.2, 128.8, 127.2, 127.0, 62.0, 54.6, 39.9, 35.4, 32.7, 27.1; MS (*m*/*z*) 291 (5) M^+, 167 (6), 124 (100), 81(16), 80 (23). Anal. Calcd for $C_{20}H_{21}NO$, C, 82.44; H, 7.26; N, 4.81. Found: C, 82.32; H, 7.24; N, 4.79.

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Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.