ORGANIC LETTERS

2005
Vol. 7, No. 9
1725−1727

Rhodium-Catalyzed Intramolecular Conjugate Addition of Vinylstannanes to 2,3-Dihydro-4-pyridones. An Efficient Route to Stereoselective Construction of Indolizidines

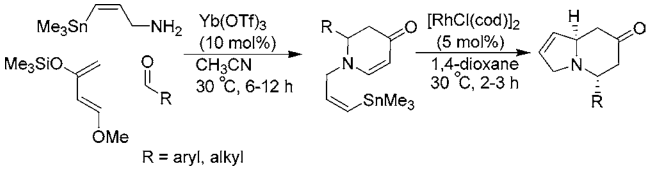
Magdalena Dziedzic, Marta Małecka, and Bartłomiej Furman*

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

furbar@icho.edu.pl

Received February 2, 2005

ABSTRACT



$[RhCl(cod)]_2$ is an effective catalyst for the intramolecular conjugate addition of vinylstannanes to 2,3-dihydro-4-pyridones under neutral conditions at room temperature. The reaction occurs in good yields, giving indolizidine skeletons with excellent diastereoselectivity. A stereochemical outcome observed in these cyclizations is proposed.

The conjugate addition of organometallic reagents to activated alkenes is an important process for carbon−carbon bond formation.[1] The use of metal catalysts in combination with an organometallic reagent has been particularly effective. Such reactions are typically carried out using organocopper reagents,[2] but reports describing the application of other metals have also appeared.[3] In 1997, Miyaura showed that organoboronic acids could be used for the conjugate addition to α,β-unsaturated ketones under catalysis by a rhodium(I) complex.[4] Furthermore, Li and later Inoue and Oi have described that rhodium complexes catalyze the coupling of α,β-unsaturated carbonyl compounds with organostannanes[5] and organosiloxanes.[6] In these catalytic reactions, the transmetalation between such organometallic reagents and a rhodium complex has been proposed as a key step of the catalytic cycle.

In connection with our interest in the synthesis of azabicyclic ring systems,[7] herein for the first time we report a general and highly stereoselective approach to the construction of indolizidine ring skeletons, based on intramolecular conjugate addition of vinylstannanes to 2,3-dihydro-4-pyridones catalyzed by a rhodium(I) complex (Scheme 1).

We assumed that the treatment of a dihydropyridone of the type **1** with vinylstannane located in the side-chain with

---

(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

(2) (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Lipshutz, B. H. In *Organometallics in Synthesis*, 2nd ed.; Schlosser, M., Ed.; Wiley: New York, 2002; pp 665−815.

(3) For nickel catalysis with organozinc reagents, see: (a) Petrier, C.; Barbosa, J. C. S.; Dupuy, C.; Luche, J.-L. *J. Org. Chem.***1985**, *50*, 5761. (b) Soai, K.; Hayasaka, Y.; Ugajin, S. *J. Chem. Soc., Chem. Commun*. **1989**, 516. For palladium catalysis with arylmercurials, see: (c) Cacchi, S.; Misiti, D.; Palmieri, G. *Tetrahedron* **1981**, *37*, 2941. For palladium catalysis with arylstannanes, see: (d) Ohe, T.; Wakita, T.; Motofusa, S.; Cho, C. S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 2149. For palladium catalysis with arylboranes, see: (e) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem*. **1995**, *60*, 883. (f) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768.

(4) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

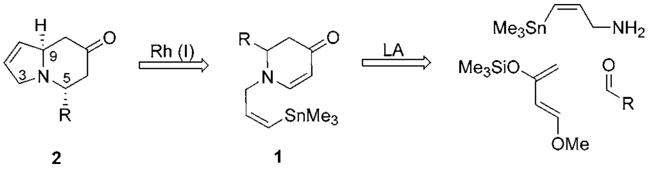
(5) (a) Oi, S.; Moro. M.; Ono, S.; Inoue, Y. *Chem. Lett.* **1998**, 83. (b) Huang, T.; Meng, Y.; Venkatraman, S.; Wang, D.; Li, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 7451. (c) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91.

(6) (a) Huang, T. S.; Li, C. J. *J. Chem. Soc., Chem. Commun.* **2001**, 2348. (b) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667.

(7) Furman, B.; Dziedzic, M. *Tetrahedron Lett.* **2003**, *44*, 6629.

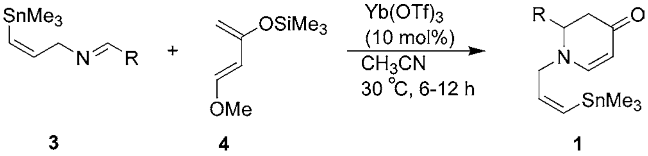
10.1021/ol050215j CCC: $30.25

Scheme 1. Synthetic Strategy



rhodium complex would result in the cyclization leading to an indolizidine skeleton **2**. The desired cyclocondensation precursors **1** should be accessible via Lewis acid mediated tandem Mannich/Michael addition of a Schiff base **3** with an electron-rich silyloxy diene **4** (Table 1).

Table 1. Lewis Acid Mediated Synthesis of 2-Substituted Dihydro-4-pyridones[a]



entry	R	yield, %[b]
1	Ph	87
2	*p*-MePh	92
3	*p*-MeOPh	85
4	*p*-ClPh	90
5	2-furyl	78
6	$PhCH_2OCH_2$	89
7	*i*-C_3H_7	69
8	*c*-C_6H_{11}	72

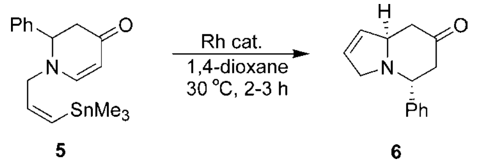
[a] Common reaction conditions: **3** (1.0 mmol), **4** (1.2 mmol), Yb(OTf)$_3$ (0.1 mmol), 10 mL solvent, 30 °C, 6−12 h. [b] Isolated yields.

As shown in Table 1, various types of aromatic and aliphatic imines were cleanly and rapidly converted to the corresponding 2-substituted 2,3-dihydropyridones **1** in the presence of 10 mol % of Yb(OTf)$_3$.[7] This reaction can also be realized as a three-component tandem Mannich/Michael process with the in situ generated imine. Although the yields in the latter case were somewhat lower than those obtained by the reaction of the preformed and isolated aldimines, the direct synthesis of dihydropyridones is advantageous in large-scale reactions.

Table 2 shows the catalytic activity of rhodium complexes in the intramolecular conjugate addition of vinylstannane to 2,3-dihydro-4-pyridones.

Of the rhodium catalysts screened, the neutral rhodium complex [RhCl(cod)]$_2$ was the most successful (entry 3). We found that treatment of 2-phenyl 2,3-dihydropyridone **5** with 5 mol % of [RhCl(cod)]$_2$ in dioxane gave unsaturated indolizidine **6** in 84% yield as a single detectable isomer. Other rhodium(I) complexes did not show activity as good as that of [RhCl(cod)]$_2$, furnishing products in a lower yield under similar conditions (entries 1, 2, and 4). On the other hand, the rhodium(I)−norbornadiene complex (entry 6) or [Rh(cod)$_2$]OTf did not catalyze the reaction at all. The addition of the phosphine ligands such as PPh$_3$ (entry 7) or dppp (entry 8) under the conditions of entry 2 did not affect the cyclocondensation to afford **6**. Unexpectedly, aqueous dioxane did not increase the yield (entry 9), which is in sharp contrast to the rhodium-catalyzed reaction of arylstannanes with enones.[5] However, the best results of cyclocondensation were obtained under an aerobic condition[8] in dioxane from a commercial source.

Table 2. Optimization of the Rhodium-Catalyzed Intramolecular Conjugate Addition of Vinylstannane to 2-Phenyl Dihydro-4-pyridone[a]



entry	catalyst	yield, %[b]
1	$[Rh(cod)(MeCN)_2]BF_4$	78
2	$[RhCl(C_2H_4)]_2$	80
3	$[RhCl(cod)]_2$	84
4	$[Rh(cod)_2]BF_4$	26
5	$[Rh(cod)_2]OTf$	0
6	$[RhCl(nbd)]_2$	0
7[c]	$[RhCl(cod)]_2$	35
8[d]	$[RhCl(cod)]_2$	30
9[e]	$[RhCl(cod)]_2$	80

[a] Common reaction conditions: **5** (0.5 mmol), rhodium catalyst (0.025 mmol), 4 mL solvent, 30 °C, 2−3 h. [b] Isolated yields. [c,d] PPh$_3$ or dppp (5 mol %) was used. [e] The reaction was conducted in dioxane/H$_2$O (10:1)

Having optimized conditions in hand, that is, 5.0 mol % [RhCl(cod)]$_2$ as catalyst in dioxane at room temperature, the scope of the reaction was then examined. Some representative results are summarized in Table 3.

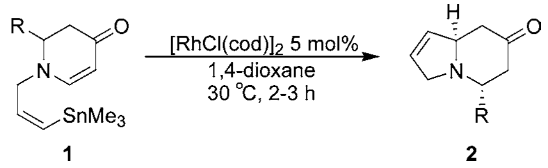
In most entries, good yields were obtained for the rhodium-catalyzed addition using a range of different 2-substituted 2,3-dihydro-4-pyridones. We observed no appreciable difference in the yield of the reaction for aromatic or aliphatic groups at C-2; however, the furyl group retarded cyclization (entry 5).

Homo- and heteronuclear correlation spectroscopies and differential NOE experiments allowed us to unambiguously establish the stereochemical pattern of our indolizidines. For a selected indolizidine (Table 3, entry 8) the multiplet at δ 4.31 ppm was assigned to the proton at C-9 and the double quartet at δ 3.96 ppm (^3J = 1.8 and 13.8 Hz) and the multiplet at 3.52 ppm and the multiplet at δ 2.93 ppm were attributed to H-3α, H-3β, and H-5, respectively. The difference in chemical shifts of the methylene protons at C-3 can

---

(8) For rhodium-catalyzed C−C bond formation in air and water, see: (a) Li, C. J.; Meng, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9538. (b) Venkatraman, S.; Li, C. J. *Tetrahedron Lett.* **2001**, *42*, 781. (c) Ding, R.; Ge, C. S.; Chen, Y. J.; Wang. D.; Li, C. J. *Tetrahedron Lett.* **2002**, *43*, 7789. (d) Ding, R.; Zhao, C. H.; Chen, Y, J.; Liu, L.; Wang, D.; Li, C. J. *Tetrahedron Lett.* **2004**, *45*, 2995.

Table 3. Rhodium-Catalyzed Cyclizations of Dihydropyridones **1**[a]



entry	R	yield, %[b]
1	Ph	84
2	*p*-MePh	86
3	*p*-MeOPh	82
4	*p*-ClPh	79
5	2-furyl	43 (86)[c]
6	$PhCH_2OCH_2$	90
7	*i*-C_3H_7	80
8	*c*-C_6H_{11}	77

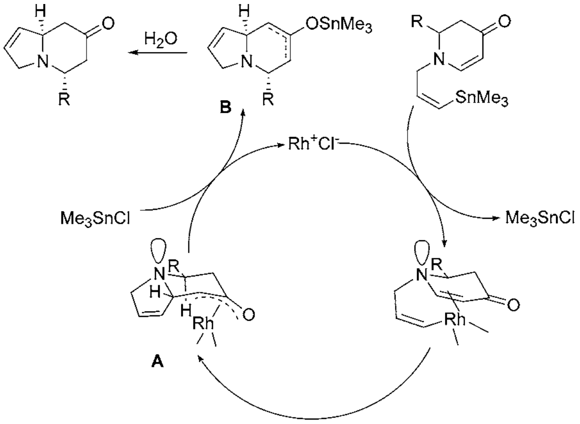
[a] Common reaction conditions: **1** (0.5 mmol), rhodium catalyst (0.025 mmol), 4 mL solvent, 30 °C, 2−3 h. [b] Isolated yields. [c] After stirring for 12 h.

be rationalized in terms of magnetic anisotropy of the nitrogen lone-pair, which causes shielding of the *syn* proton and deshielding of the *anti* proton. This pattern for the methylene group at C-3 is consistent with available literature precedents for the indolizidine system.[9] Upon irradiation of the multiplet at δ 2.93 ppm (H-5) no enhancement was observed for the multiplet at δ 4.31 ppm (H-9), whereas 3.3% enhancement was observed for the multiplet δ 3.52 ppm (H-3β). These observations could only be reconciled by assumption of the *trans*-orientation between H-5 and H-9 protons.

A plausible catalytic cycle, based on the original proposal by Inoue and Oi[5a] and the stereochemical outcome observed in these cyclizations, is rationalized in Scheme 2.

The initial step of the catalytic cycle should consist of the transmetalation of the vinylstannane group to a Rh(I) species followed by coordination of the dihydropyridone moiety. The 1,4-insertion of the vinylrhodium species takes place exclusively *anti* to the R substituent located in the equatorial position, leading to compound **A** with *trans*-orientation between the C5 and C9 protons. The intermediate **A** is trapped by the catalytically generated trimethyltin chloride to give tin enolate **B**. Protonolysis of the enolate **B** furnishes the conjugate addition product.

Scheme 2. Proposed Catalytic Cycle



In conclusion, a novel stereoselective approach to unsaturated indolizidines has been described involving the Lewis acid mediated tandem Mannich/Michael reaction and rhodium-catalyzed intramolecular conjugate addition of vinylstannanes to dihydropyridones. Further work is currently in progress to apply this new method to the diastereo- and enantioselective synthesis of indolizidine systems.

Acknowledgment. We wish to thank the State Committee for Scientific Research (Grant 4 T09A 064 25) for support of this work.

Supporting Information Available: Representative experimental procedures with spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050215J

---

[9] (a) Fleurant, A.; Saliou, C.; Célérier, J. P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem.* **1995**, *32*, 255. (b) Michael, J. P.; Gravestock, D. *Eur. J. Org. Chem.* **1998**, 865.