ORGANIC LETTERS

2004
Vol. 6, No. 16
2785−2788

Synthesis of Five-, Six-, and Seven-Membered Ring Lactams by Cp*Rh Complex-Catalyzed Oxidative N-Heterocyclization of Amino Alcohols

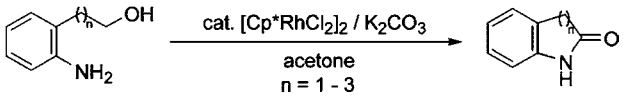
Ken-ichi Fujita,* Yoshinori Takahashi, Maki Owaki, Kazunari Yamamoto, and Ryohei Yamaguchi*

Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

fujitak@kagaku.mbox.media.kyoto-u.ac.jp

Received June 1, 2004

ABSTRACT



A new effective catalytic system consisting of $[Cp^*RhCl_2]_2/K_2CO_3$ (Cp* = pentamethylcyclopentadienyl) for the lactamization of amino alcohols has been developed. As an example, the reaction of 3-(2-aminophenyl)-1-propanol in the presence of $[Cp^*RhCl_2]_2$ (5.0% Rh) and K_2CO_3 (10%) in acetone gives 3,4-dihydro-2(1*H*)-quinolinone in an isolated yield of 80%. A variety of five-, six-, and seven-membered benzo-fused lactams are synthesized by this catalytic system.

The benzo-fused lactam skeleton is an important element in a number of pharmacologically and biologically active compounds. Particularly, oxindole, dihydroquinolinone, and tetrahydrobenzazepinone derivatives are found in many natural products, marketed drugs, and drug candidates.[1] In this context, it is quite important to develop an efficient method for the synthesis of these compounds. Although a number of noncatalyzed,[2] transition metal-catalyzed,[3,4] photochemical,[5] and radical-mediated[6] reactions for the synthesis of oxindoles have been developed, there have been only a few examples of simple and efficient catalytic synthesis of tetrahydroquinolinones and tetrahydrobenzazepinones.[7]

We are currently studying the catalytic activity of group 9 metals bearing pentamethylcyclopentadienyl (Cp*) ligands toward hydrogen-transfer reactions[8,9] and have reported intramolecular N-alkylation of amino alcohols catalyzed by a Cp*Ir complex (eq 1, left arrow).[8b] During the investigation

(1) (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Oshiro, Y.; Sakurai, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Miwa, T.; Nishi, T. *J. Med. Chem.* **2000**, *43*, 177. (c) Zhao, H.; Thurkauf, A.; Braun, J.; Brodbeck, R.; Kieltyka, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2119. (d) Tamura, S. Y.; Goldman, E. A.; Bergum, P. W.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2573. (e) Murakami, Y.; Hara, H.; Okada, T.; Hashizume, H.; Kii, M.; Ishihara, Y.; Ishikawa, M.; Shimamura, M.; Mihara, S.; Kato, G.; Hanasaki, K.; Hagishita, S.; Fujimoto, M. *J. Med. Chem.* **1999**, *42*, 2621. (f) Jossang, A.; Jossang, P.; Hadi, H. A.; Sévenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527. (g) Wiseman, E. H.; Chiaini, J.; McManus, J. M. *J. Med. Chem.* **1973**, *16*, 131.

(2) Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093 and references therein.

(3) Palladium-catalyzed reactions: (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (c) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193. (d) Lee, S.; Hartwig, J. F. J. *Org. Chem.* **2001**, *66*, 3402. (e) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (f) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488. (g) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.

(4) Rhodium-catalyzed reactions: (a) Hirao, K.; Morii, N.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* **1995**, *36*, 6243. (b) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (c) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017.

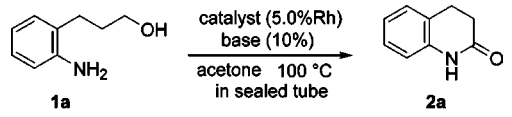
(5) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435.

(6) (a) Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657. (b) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657.

(7) (a) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (b) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (c) Ali, B. E.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264. (d) Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673.

10.1021/ol0489954 CCC: $27.50
Published on Web 07/07/2004

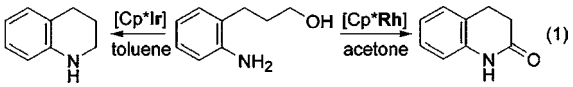
Table 1. Synthesis of 3,4-Dihydro-2(1*H*)-quinolinone (**2a**) from 3-(2-Aminophenyl)-1-propanol (**1a**) under Various Catalytic Conditions[a]



entry	catalyst	base	yield[b] (%)
1	$[Cp^*RhCl_2]_2$	K_2CO_3	81
2[c]	$[Cp^*RhCl_2]_2$	K_2CO_3	62
3[d]	$[Cp^*RhCl_2]_2$	K_2CO_3	72
4[e]	$[Cp^*RhCl_2]_2$	K_2CO_3	f
5	$Cp^*Rh(OAc)_2 \cdot H_2O$	K_2CO_3	28
6	$RhCl(PPh_3)_3$	K_2CO_3	43
7	$[RhCl(CO)_2]_2$	K_2CO_3	0
8	$[Cp^*RhCl_2]_2$	Na_2CO_3	46
9	$[Cp^*RhCl_2]_2$	Et_3N	0

[a] Reaction was carried out in a heavy-walled glass reactor at 100 °C for 20 h with **1a** (0.50 mmol), catalyst (5.0% Rh), and base (10%) in acetone (12.5 mL). [b] Determined by GC. [c] Reaction temperature was 80 °C. [d] Amount of acetone was 6.3 mL. [e] Reaction was carried out in toluene (12.5 mL) instead of acetone. [f] 1,2,3,4-Tetrahydroquinoline (32%) was isolated in addition to a small amount of **2a** (ca. 5%).

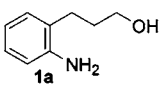
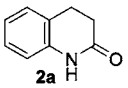
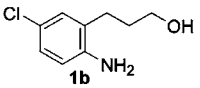
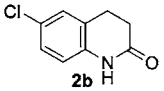
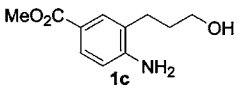
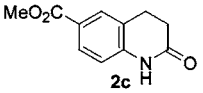
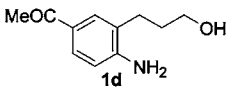
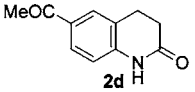
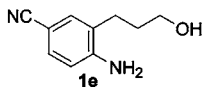
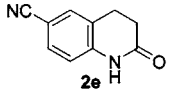
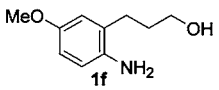
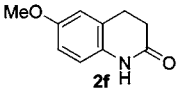
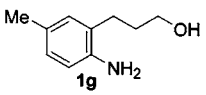
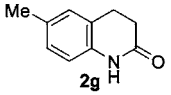
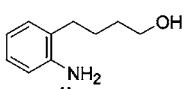
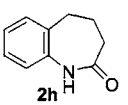
on this reaction in further detail, we found that intramolecular lactamization proceeded instead of N-alkylation when the reaction was carried out with Cp*Rh catalyst in acetone (eq 1, right arrow). This result prompted us to develop this catalytic lactamization system into the synthesis of a variety of benzo-fused lactams. To the best of our knowledge, there has been only one report on the transformation of amino alcohols to lactams by the transition metal-catalyzed hydrogen transfer reactions.[10] In this paper, we report a new and efficient method for the synthesis of five-, six-, and seven-membered benzo-fused lactams catalyzed by a Cp*Rh complex.



First, we investigated oxidative N-heterocyclization of 3-(2-aminophenyl)-1-propanol (**1a**) under various conditions. The reactions were performed in the presence of several rhodium complexes and bases in acetone as a solvent. The results are summarized in Table 1. When the reaction was performed at 100 °C for 20 h in the presence of $[Cp^*RhCl_2]_2$ (0.0125 mmol, 5.0% Rh) and K_2CO_3 (0.050 mmol, 10%) in acetone (12.5 mL), 3,4-dihydro-2(1*H*)-quinolinone (**2a**) was formed in 81% yield (entry 1). In this reaction, lactamization proceeded selectively; other products such as 1,2,3,4-tetrahydroquinoline or quinoline were not detected. A lower reaction temperature (80 °C) resulted in a lower yield of **2a** (entry 2). When the amount of acetone was reduced to 6.3 mL, the yield of **2a** slightly decreased (entry 3). When the reaction was performed in toluene as a solvent instead of acetone, 1,2,3,4-tetrahydroquinoline was formed in 32% yield in addition to a very small amount of **2a** (ca. 5%)(entry 4). These results clearly indicate that acetone plays a key role as a hydrogen acceptor. Other rhodium catalysts, $Cp^*Rh(OAc)_2 \cdot H_2O$, $RhCl(PPh_3)_3$, and $[RhCl(CO)_2]_2$, showed lower activity than $[Cp^*RhCl_2]_2$ (entries 5−7).[11] The yield of **2a** considerably decreased when the reaction was performed in the presence of Na_2CO_3 or triethylamine as a base instead of K_2CO_3 (entries 8 and 9).

On the basis of these results, we next examined the synthesis of various six- and seven-membered benzo-fused lactams under the optimized conditions. The results are summarized in Table 2. 3-(2-Aminophenyl)propanols (**1b**−

Table 2. Synthesis of Various Six- and Seven-Membered Benzo-Fused Lactams from Amino Alcohols Catalyzed by the $[Cp^*RhCl_2]_2/K_2CO_3$ System[a]

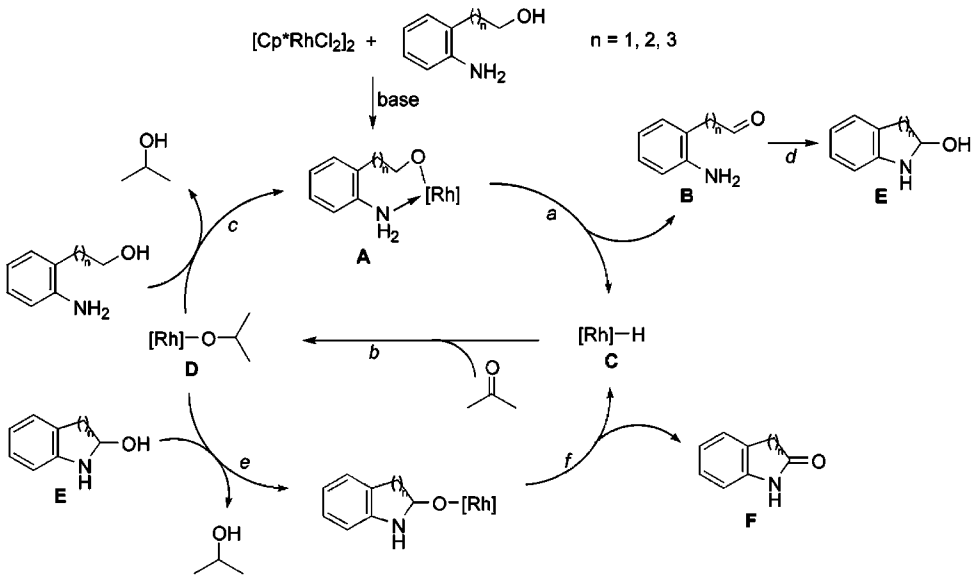
entry	substrate	product	yield[b]
1			80
2			96
3			97
4			96
5[c]			71
6[d]			63
7			96
8[e]			86

[a] Reaction was carried out in a heavy-walled glass reactor at 100 °C for 20 h with amino alcohol (0.50 mmol), $[Cp^*RhCl_2]_2$ (5.0% Rh), and K_2CO_3 (10%) in acetone (12.5 mL). [b] Isolated yield. [c] Reaction time was 30 h. [d] $[Cp^*RhCl_2]_2$ (9.8% Rh) was used as a catalyst. [e] $[Cp^*RhCl_2]_2$ (10.5% Rh) was used as a catalyst.

(8) (a) Fujita, K.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289. (b) Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, *4*, 2691. (c) Fujita, K.; Owaki, M.; Yamaguchi, R. *Chem. Commun.* **2002**, 2964. (d) Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687. (e) Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2004**, *23*, 1490. (f) Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* **2004**, *45*, 3215.

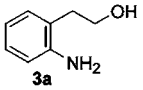
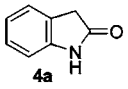
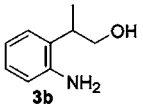
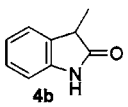
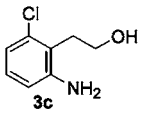
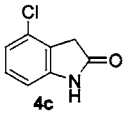
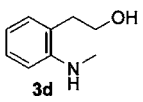
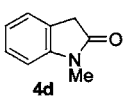
(9) Some other groups have reported hydrogen-transfer reductive amination reactions catalyzed by group 9 metal (Rh, Ir) complexes bearing a Cp* ligand. (a) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. (b) Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, *67*, 8685. (c) Ogo, S.; Makihara, N.; Kaneko, Y.; Watanabe, Y. *Organometallics* **2001**, *20*, 4903.

Scheme 1



g) bearing a substituent on the aromatic ring were converted into the corresponding 3,4-dihydro-2(1*H*)-quinolinones (**2b**−**g**) in moderate to excellent yields, respectively (entries 2−7). With substrates bearing an electron-withdrawing substituent (Cl, CO_2Me, and COMe), the yields of the products were excellent (entries 2−4). In the case of the substrate **1e** bearing a CN substituent, the yield of the product **2e** was relatively low (71%) even with a longer reaction time (30 h), which is possibly due to the deactivation of the catalyst by the coordination of CN substituent to the rhodium center (entry 5). In the case of the substrate **1f** bearing the electron-donating OMe substituent, the yield of the product **2f** was moderate (63%) even with a higher catalyst loading (9.8% Rh) (entry 6). It should be noted that the present catalytic system was applicable to the synthesis of 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (**2h**) using 4-(2-aminophenyl)-1-butanol (**1h**) as a starting material (entry 8).

Table 3. Synthesis of Oxindoles from Amino Alcohols Catalyzed by the $[Cp^*RhCl_2]_2/K_2CO_3$ System[a]

entry	substrate	cat.(%Rh)	product	yield[b]
1	 **3a**	3.0	 **4a**	74
2[c]	 **3b**	3.0	 **4b**	80
3[d]	 **3c**	3.2	 **4c**	52
4[c]	 **3d**	6.0	 **4d**	46

[a] Reaction was carried under reflux for 8 h with amino alcohol (1.0 mmol), $[Cp^*RhCl_2]_2$, and K_2CO_3 (10%) in acetone (20 mL). [b] Isolated yield. [c] Reaction was carried out in 0.50 mmol scale. [d] Reaction time was 20 h.

Synthesis of five-membered benzo-fused lactams (oxindoles) was also examined. The results are summarized in Table 3. 2-Aminophenethyl alcohols (**3a**−**d**) bearing a substituent on the aromatic ring, the methylene chain, and the nitrogen atom were converted into the corresponding oxindoles (**4a**−**d**) in moderate to high yields, respectively. In contrast to the synthesis of dihydroquinolinones and tetrahydrobenzazepinone, the synthesis of oxindoles could be carried out at a lower temperature (acetone reflux) with a lower catalyst loading (3.0% Rh). Reaction of 2-aminophenethyl alcohol (**3a**) in the presence of $[Cp^*RhCl_2]_2$ (3.0% Rh) and K_2CO_3 (10%) in acetone (20 mL) under reflux for 8 h gave oxindole (**4a**) in 74% yield (entry 1). In this reaction, a small amount of indole (10%) was also formed. Reaction of 2-(2-aminophenyl)-1-propanol (**3b**) gave 3-methyloxindole (**4b**) in good yield (80%) (entry 2). Oxindoles bearing a substituent at the aromatic ring or the nitrogen atom could be also synthesized; however, the yields were relatively low (entries 3 and 4).

Although the mechanism for the present reaction is not completely clear yet, a possible one is shown in Scheme 1.[12] The first step of the reaction would involve the coordination of amino alcohol to the rhodium center to give an intermediate **A**. Then, β-hydrogen elimination would occur to give

(10) Ruthenium-catalyzed oxidative N-heterocyclizations of amino alcohols to lactams have been reported. In these reactions, a higher reaction temperature (140 °C) and addition of excess benzalacetone as a hydrogen acceptor are required, and applicable amino alcohols are highly restricted. Naota, T.; Murahashi, S.-I. *Synlett* **1991**, 693.

(11) Reaction of **1a** (0.50 mmol) at 100 °C for 20 h in the presence of $[Cp^*IrCl_2]_2$ (0.0127 mmol, 5.1% Ir) and K_2CO_3 (0.050 mmol, 10%) in acetone (12.5 mL) gave **2a** in 59% yield.

an amino-aldehyde **B** and a rhodium hydride species **C** (step *a*). Insertion of acetone into the rhodium−hydride bond in **C** would occur to give a rhodium isopropoxide species **D** (step *b*), which is subject to the alkoxy exchange reaction with amino alcohol to regenerate **A** (step *c*). Concurrently, the intermediate **B** would undergo condensation to give a cyclic hemiaminal **E** (step *d*). Oxidation of **E** by the rhodium catalyst via β-hydrogen elimination would give the lactam product **F** (steps *e* and *f*). Thus, the Cp*Rh catalyst could play a dual role in both dehydrogenations of the alcohol as well as the hemiaminal.

In summary, we have shown a new efficient catalytic system for the synthesis of five-, six-, and seven-membered ring lactams from amino alcohols catalyzed by a Cp*Rh complex. It should be noted that selective synthesis of N-alkylated or lactamized product from the same starting materials (amino alcohols) can be achieved by altering the catalytic systems (Cp*Rh in acetone or Cp*Ir in toluene[8b]). Investigations in further detail about the differences of catalytic activities of Cp*Rh and Cp*Ir complexes are now in progress, which we will disclose in due course.

(12) First step in this mechanism is similar to that we have proposed for the intramolecular cyclization of amino alcohols catalyzed by a Cp*Ir complex (ref 8b). We are currently investigating in detail the differences in catalytic activities between Cp*Rh and Cp*Ir complexes, which will be disclosed in due course.

Acknowledgment. This work was supported by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (No. 14550806).

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

OL0489954