ORGANIC LETTERS

2013
Vol. 15, No. 15
3962–3965

Ruthenium-Catalyzed Carbonylative C−H Cyclization of 2-Arylphenols: A Novel Synthetic Route to 6*H*-Dibenzo[*b,d*]pyran-6-ones

Kiyofumi Inamoto,* Jun Kadokawa, and Yoshinori Kondo*

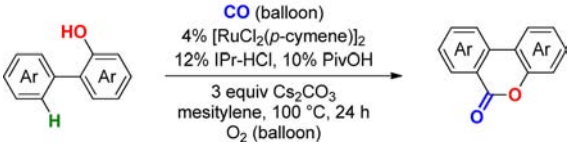
Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

inamoto@m.tohoku.ac.jp; ykondo@m.tohoku.ac.jp

Received June 20, 2013

ABSTRACT

Carbonylative C–H Cyclization



Catalytic carbonylative C−H cyclization of 2-arylphenols can be achieved in the presence of a ruthenium-based catalytic system. The process proceeds efficiently under balloon pressure of CO and produces variously substituted 6*H*-dibenzo[*b,d*]pyran-6-one compounds, typically in good to high yields. Functional groups such as the alkoxycarbonyl and acetyl groups as well as halogen atoms (F, Cl, and Br) are well tolerated during the reaction.

Since the pioneering work of Heck and co-workers in 1974,[1] transition-metal-catalyzed carbonylation of aryl/vinyl halides with carbon monoxide (CO), especially using a palladium (Pd)-based catalytic system, has witnessed tremendous improvements in the synthesis of carbonyl-group-containing molecules.[2] On the other hand, despite recent significant progress in transition-metal-catalyzed C−H functionalization, there have only been limited examples utilizing CO for catalytic C−H carbonylation, in which palladium has also played a pivotal role.[3] C(sp^2)−H carbonylation of simple arenes was first developed by Fujiwara et al. using a Pd catalyst.[4,5] In 2004, Orito reported on alkylamine-directed, Pd-catalyzed *ortho* C(sp^2)−H carbonylation, which provided facile access to five- or six-membered benzolactams.[6a] Thereafter, several procedures for directing group-assisted C−H carbonylation were established, providing efficient routes to carboxylic acids and their derivatives regioselectively.[6b–j,7] In our research on the construction of heterocyclic compounds

(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331. (c) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764.

(2) For recent reviews, see: (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114–4133. (b) Grigg, R.; Mutton, S. P. *Tetrahedron* **2010**, *66*, 5515–5548. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986–5009. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1–35.

(3) For a review on transition-metal-catalyzed oxidative carbonylation, see: Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788–10799.

(4) For reviews, see: (a) Fujiwara, Y.; Tabaki, K.; Taniguchi, Y. *Synlett* **1996**, 591–599. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639.

(5) Similar Pd-catalyzed carbonylation of anisoles using O_2/molybdovanadophosphate as the reoxidation system was also reported; see: Ohashi, S.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2005**, 486–488.

(6) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342–14343. (b) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082–14083. (c) Houlden, C. E.; Hutchby, M.; Bailey, C.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830–1833. (d) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686–693. (e) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378–17380. (f) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, *39*, 10442–10446. (g) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312–315. (h) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326–5329. (i) Albert, J.; Ariza, X.; Calvet, T.; Font-Bardia, M.; Garcia, J.; Granell, J.; Lamela, A.; López, B.; Martinez, M.; Ortega, L.; Rodriguez, A.; Santos, D. *Organometallics* **2013**, *32*, 649–659. (j) Rajeshkumar, V.; Lee, T.-H.; Chuang, S.-C. *Org. Lett.* **2013**, *15*, 1468–1471.

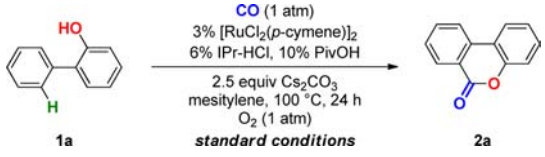
(7) For other examples of Pd-catalyzed C−H carbonylation, see: (a) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7316–7319. (b) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5240–5207.

10.1021/ol401734m © 2013 American Chemical Society
Published on Web 07/17/2013

using Pd-catalyzed C−H cyclization,[8] it was found that a ruthenium (Ru)-based catalyst is highly active for carbonylative cyclization of 2-arylphenols via C−H functionalization. This caused a novel access to 6*H*-dibenzo[*b*,*d*]pyran-6-ones, which constitute an important class of heterocycles with various biological activities.[9,10] Although Ru catalysts have recently attracted increased attention in catalytic C−H functionalization because of their remarkable reactivity and inexpensiveness compared with Pd and Rh,[11] only one catalytic system based on Ru, developed by Chatani et al., for carbonylative C−H cyclization has appeared in literature.[12−14] This catalytic system successfully induces cyclization, involving the functionalization of both C(sp^2)−H and C(sp^3)−H bonds, with the aid of a 2-pyridinylmethylamino moiety as a chelating *N*,*N*-bidentate ligand; however, the requirement of high pressure CO (10 bar) and ethylene (7 bar) as well as harsh reaction conditions (160 °C in toluene) may be certain drawbacks to its applicability. Our procedure employs a catalytic combination of Ru/N-heterocyclic carbene (NHC)[15] with a balloon pressure of CO and O_2 and successfully promotes the carbonylative C−H cyclization under relatively mild conditions (100 °C in mesitylene). Yields are generally good to high, and good functional group compatibility (e.g., the alkoxycarbonyl and acetyl groups, halogen atoms) is observed during the process. Herein, the details of this procedure are described.

At the beginning of the study on carbonylative C−H cyclization of 2-phenylphenol **1a** (Table 1),[16] the catalytic activities of several transition metals were evaluated, and the conclusion was that the Ru catalyst is superior to others. It was determined that the combination of [$RuCl_2$(*p*-cymene)]$_2$/IPr along with PivOH[17] serves as an effective catalyst for cyclization. Using the catalytic system, the reaction of **1a** in mesitylene solvent, in the presence of Cs_2CO_3 as a base under 1 atm of CO and O_2 pressure, smoothly proceeded, providing the desired product **2a** in fairly good yield (entry 1). Other metals, including Pd, are less active in the process (entry 2). In the absence of [$RuCl_2$(*p*-cymene)]$_2$, IPr, or PivOH, little or no carbonylative C−H cyclization occurred (entries 3−5). Moreover, the reaction without O_2 resulted in the quantitative recovery of **1a**, suggesting that O_2 effectively functions as a reoxidant in the dibenzopyranone synthesis (entry 6). Phosphine ligands were completely inactive (entry 7), and the use of NHC ligands, except IPr, led to lower yields (entry 8). Among the bases tested, Cs_2CO_3 was optimal (entry 9); from solvent screening, mesitylene proved to be the best (entry 10). Subsequent examination revealed that the utilization of balloon pressure of both CO and O_2 increased the yield of **2a** (entry 11). Ultimately, fine-tuning of the catalyst loading led to the determination of the optimal conditions for catalyzation, 4% [$RuCl_2$(*p*-cymene)]$_2$ and 12% IPr.

Table 1. Effect of Reaction Parameters



1a **2a**

entry	variation from standard conditions	yield (%)[a,b]
1	none	45
2[c]	"Pd," "Rh," or "Cu," instead of "Ru"	(0−25)
3	without [$RuCl_2$(*p*-cymene)]$_2$	0
4	without IPr	0
5	without PivOH	30
6[c]	without O_2	0
7	PPh_3, P(*o*-tol)$_3$, or dppf, instead of IPr	0
8	IMes-HCl, SIPr-HCl, SIMes-HCl, IAd-HCl, or I^{t}Bu-HCl, instead of IPr-HCl	(7−43)
9	K_2CO_3, NaOAc, KOMe, KF, LiHMDS, instead of Cs_2CO_3	(0−18)
10	toluene, DMSO, NMP, 2-PrOH, or AcOH, instead of mesitylene	(0−32)
11	with CO and O_2 balloons	68
12[d]	4% [$RuCl_2$(*p*-cymene)]$_2$ and 12% IPr with CO and O_2 balloons	88

[a] Isolated yields. [b] Yields determined by GC analysis versus a calibrated internal standard in parentheses. [c] 5% transition metal, 10% IPr, and 50% PivOH were used. [d] 3 equiv of Cs_2CO_3 was used.

(8) (a) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931–2934. (b) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147–5150. (c) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *Synlett* **2008**, 3157–3162. (d) Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Commun.* **2008**, 5529–5531. (e) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900–3903. (f) Inamoto, K.; Hasegawa, C.; Kawasaki, J.; Hiroya, K.; Doi, T. *Adv. Synth. Catal.* **2010**, *352*, 2643–2655. (g) Inamoto, K.; Kawasaki, J.; Hiroya, K.; Kondo, Y.; Doi, T. *Chem. Commun.* **2012**, *48*, 4332–4334. (h) Inamoto, K.; Nozawa, K.; Kondo, Y. *Synlett* **2012**, *23*, 1678–1682.

(9) The 6*H*-dibenzo[*b*,*d*]pyran-6-one framework exists in several natural products such as Gilvocarcins; see: Hou, J.; Liu, P.; Qu, H.; Fu, P.; Wang, Y.; Wang, Z.; Li, Y.; Teng, X.; Zhu, W. *J. Antibiot.* **2012**, *65*, 523–526 and references therein.

(10) For the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones, see: James, C. A.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4080–4093 and references therein.

(11) For reviews on Ru-catalyzed C−H functionalization, see: (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918. (b) Ackermann, L. *Acc. Chem. Res.* **2013**, *46*, ASAP (DOI: 10.1021/ar3002798).

(12) (a) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898–6899. (b) Hasegawa, N.; Charra, V.; Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070–8073. (c) Shibata, K.; Hasegawa, N.; Fukumoto, Y.; Chatani, N. *ChemCatChem* **2012**, *4*, 1733–1736.

(13) For directing-group-assisted, Ru-catalyzed aromatic C(sp^2)−H acylation in the presence of CO and alkenes, see: (a) Moore, E. J.; Pretzer, W. R.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888–5890. (b) Imoto, S.; Uemura, T.; Kakiuchi, F.; Chatani, N. *Synlett* **2007**, 170–172 and references therein.

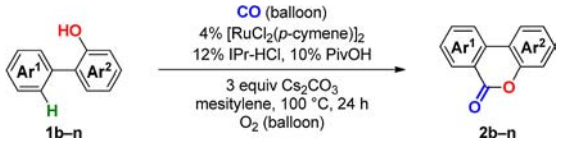
(14) For a review on Ru-catalyzed carbonylation, see: Wu, X.-F.; Neumann, H. *ChemCatChem* **2012**, *4*, 447–458.

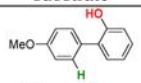
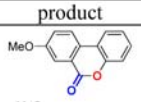
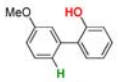
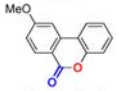
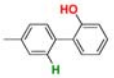
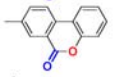
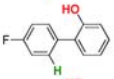
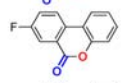
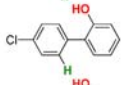
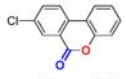
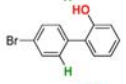
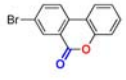
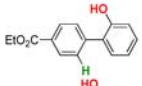
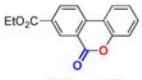
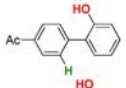
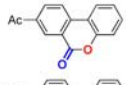
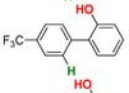
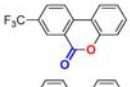
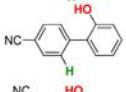
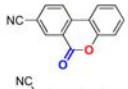
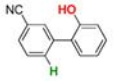
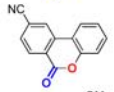
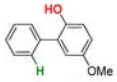
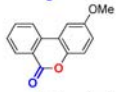
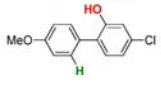
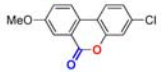
(15) The Ru/NHC catalyst system was previously employed for the C−H arylation of 2-pyridylbenzene, see: (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (b) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouene, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157.

(16) For the synthesis of dibenzofurans via Pd-catalyzed C−H functionalization/intramolecular C−O formation of 2-arylphenols, see: (a) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250–9253. (b) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504–5507.

(17) Ackermann has extensively studied the positive effect of carboxylates in Ru-catalyzed C−H functionalization processes; see: Reference 11b.

Table 2. Substrate Scope of 6*H*-Dibenzo[*b*,*d*]pyran-6-ones Synthesis



entry	substrate	1	product	2	yield (%)[a]
1		1b		2b	89
2		1c		2c	96
3		1d		2d	94
4		1e		2e	55
5		1f		2f	0
6		1g		2g	56[b]
7		1h		2h	62
8		1i		2i	77
9		1j		2j	79[b]
10		1k		2k	81
11		1l		2l	83
12		1m		2m	28[b]
13		1n		2n	trace
14		1o		2o	65
15		1p		2p	55

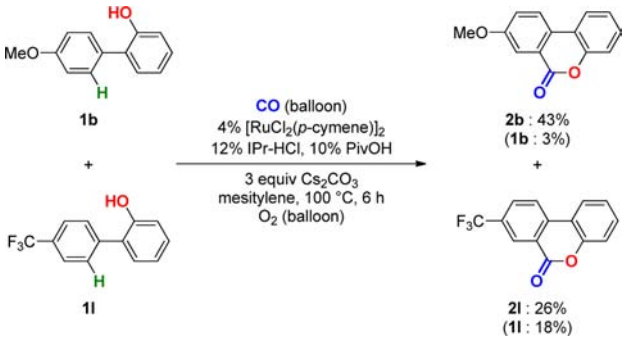
[a] Yields of isolated products. [b] With 8% $[RuCl_2(p\text{-cymene})]_2$ and 24% IPr-HCl.

Under these conditions, dibenzopyranone **2a** was produced in high yields (88%, entry 12).[18]

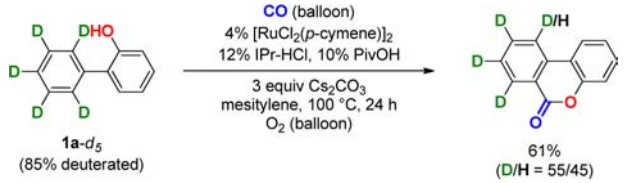
Once an efficient catalytic system was developed, the substrate scope of the method was investigated (Table 2). The process generally tolerates various substituents on the benzene ring, such as the electron-donating methoxy group (entries 1, 2, 14, and 15) and the electron-withdrawing alkoxycarbonyl, acetyl, and trifluoromethyl groups (entries 9–11). It is also noteworthy that halogen atoms (F, Br, and Cl) were compatible during the process (entries 6–8 and 15). The reactions of substrates which possess a substituent at the *meta* position on Ar^1 (**1c** and **1e**) occurred regioselectively at the less sterically hindered 6-position; the corresponding dibenzopyranones (**2c** and **2e**) were obtained exclusively, and no regioisomers were observed (entries 2 and 4). On the other hand, the reactions of **1d**, bearing the methyl group at the *ortho* position on Ar^1, and **1k** and **1l**, possessing the electron-withdrawing cyano group, were rather sluggish, resulting in a large recovery of the starting materials (entries 5, 12, and 13).

Although the precise reaction mechanism of the process remains unclear, several preliminary mechanistic studies have been performed. An intermolecular competition experiment using **1b** and **1l** suggested that electron-rich substrates are more reactive (**2b**:**2l** ≈ 1.7:1, Scheme 1). In addition, the catalytic C–H cyclization of the isotopically labeled **1a**-d_5 revealed that the C–H metalation step is reversible (Scheme 2). A similar H/D exchange has previously been reported in Ru-catalyzed C–H arylation and aroylation.[19]

Scheme 1. Intermolecular Competition Experiment



Scheme 2. C–H Cyclization of Labeled **1a**-d_5



In summary, we have developed a new Ru-based catalytic system that successfully effects carbonylative C–H cyclization of 2-arylphenols to produce 6*H*-dibenzo[*b*,*d*]pyran-6-one compounds in good to high yields. The protocol

(18) For details on the optimization studies, see Supporting Information.

(19) (a) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **20010**, *12*, 5032–5035. (b) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664–670. (c) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6293–6297.

allows the use of balloon pressure CO and O_2 under relatively mild reaction conditions, making the method highly applicable. Further studies to broaden the substrate scope and to unveil the precise reaction mechanism of the process are underway. We are also applying this approach to the construction of other classes of heterocyclic compounds.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research (B) (No. 23390002), a Grant-in-Aid for Scientific Research (C) (No. 25460002), and a Grant-in-Aid for Challenging Exploratory Research (No. 25670002) from Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (No. 23105009) from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. Detailed experimental procedures and spectroscopic and analytical data for compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.