ORGANIC LETTERS

2012
Vol. 14, No. 16
4130–4133

A General Method for Palladium-Catalyzed Direct Carbonylation of Indole with Alcohol and Phenol

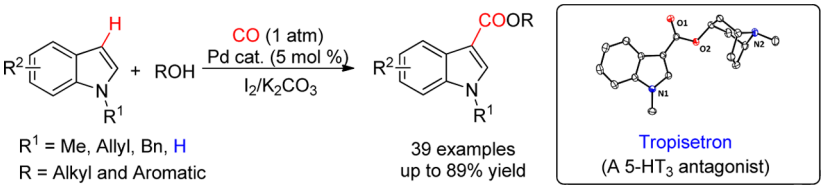
Rui Lang,[†,§] Lijun Shi,[†] Dengfeng Li,[†] Chungu Xia,[*,†] and Fuwei Li[*,†,‡]

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China, Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences, Suzhou 215123, P. R. China, and Graduate University of Chinese Academy of Sciences, Beijing 100049, P. R. China

fuweili@licp.cas.cn; cgxia@lzb.ac.cn

Received June 28, 2012

ABSTRACT



A novel strategy involving a first oxidative iodination and subsequent Pd^0-catalyzed carbonylation to yield indole-3-carboxylate has been developed. It showed perfect generality to indole, alcohol, and phenol. The current methodology could also be conveniently applied to the synthesis of biologically active tropisetron from simple indole and tropine.

General and regioselective methods for the direct functionalization of (hetero)arenes continue to be an area of intense activity, especially in the context of natural product and medicinal chemistry related substructures.[1] Recently, transition metal catalyzed, especially Pd-catalyzed, carbonylation of C−H bonds has become one of the most dominant themes for the functionalization of (hetero)arenes by the introduction of a carbonyl moiety into molecules, as it avoids the requirement of Ar−X (X = Br, I, OTs, etc.).[2,3] On the other hand, achieving good generality and regioselectivity in direct carbonylation is still problematic unless directing-group-containing arenes are employed.[4−6] Additionally, the key step in the Pd-catalyzed oxidative carbonylation of C−H bonds is the Pd^{II}-metalation, which controls the reactivity and is also inevitably challenged by the reduction of Pd^{II} to inactive Pd^0 species under a CO atmosphere. One alternative

[†] Lanzhou Institute of Chemical Physics.
[‡] Suzhou Institute of Nano-Tech and Nano-Bionics.
[§] Graduate University of Chinese Academy of Sciences.

(1) Reviews for C−H activation: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (e) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

(2) Reviews for Pd-catalyzed C−X carbonylation: (a) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402. (b) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (c) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986.

(3) Selected examples for C−X carbonylation: (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Li, Y.; Yu, Z.; Alper, H. *Org. Lett.* **2007**, *9*, 1647. (c) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. (d) Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899. (e) Siamaki, A. R.; Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1135. (f) Liu, Q.; Li, G.; He, J.; Liu, J.; Li, P.; Lei, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3371. (g) Wu, X.-F.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5284. (h) Wu, X.-F.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11142. (i) Reeves, D. C.; Rodriguez, S.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 2495. (j) Worrall, K.; Xu, B.; Bontemps, S.; Arndtsen, B. A. *J. Org. Chem.* **2011**, *76*, 170. (k) Xin, Z.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2012**, *14*, 284. (l) Li, Y.; Xue, D.; Wang, C.; Liu, Z.-T.; Xiao, J. *Chem. Commun.* **2012**, *48*, 1320. (m) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2012**, *18*, 3831.

(4) (a) Fujiwara, Y.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 220. (b) Itahara, T. *Chem. Lett.* **1982**, 1151. (c) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7316.

(5) (a) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (b) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967.

10.1021/ol3017726
Published on Web 07/27/2012

strategy to overcome these limitations could possibly be to develop a consecutive protocol under which the aryl C−H bond instead of the catalyst would be initially oxidized, regioselectively affording the functionalized intermediate that could participate in further Pd^0-catalyzed carbonylation to yield the desired carbonyl compound.

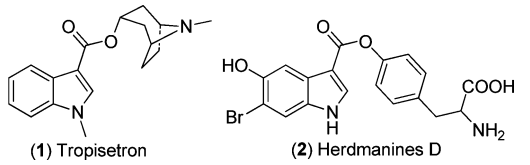
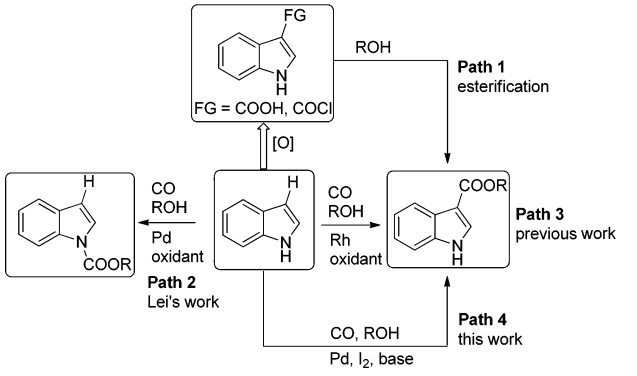


Figure 1. Representative indole-3-carboxylate derivatives with bioactivity.

The substituted indole nucleus is a structural component of a number of biologically active compounds such as tropisetron (Figure 1, compound **1**), which has been proven to act as a selective 5-hydroxytryptamine receptor ($5\text{-}HT_3$) antagonist and used to prevent chemotherapy-induced digestive side effects.[7,8] Traditionally, the preparation of indole-3-carboxylate derivatives required multistep reactions *via* its carboxylic acid or acid chloride intermediates (Scheme 1, Path 1).[9] Recently, Lei et al. developed a Pd-catalyzed direct carbonylation of *N*-substituted indole to form indole-3-carboxylate, but this carbonylation took place at the N-position to afford indole carbamates when the substrate was extended to free (NH)-indole (Path 2).[10] Meanwhile, our group also disclosed a similar oxidative carbonylation procedure to generate desired indole-3-carboxylates using the $[Rh(COD)Cl]_2/K_2S_2O_8$ catalyst system, and the substrate scope was applicable to various *N*-substituted indoles and even part of free (NH)-indole (Path 3). However, there have been far more hurdles to overcome in view of the high price of the rhodium catalyst and low yield of *N*-unprotected indole-3-carboxylates (27%−52%).[11]

Thereupon, we envision that an efficient and general Pd-catalyzed direct carbonylation of indoles to synthesize indole-3-carboxylates would be more fascinating than the existing protocols and the key issue should be regio-control, which has not been successfully resolved by a Pd catalyst system to date. Recently, Daugulis et al. reported a Cu^I/I_2 catalyzed cross-coupling of (hetero)aromatic C−H bonds with excellent regioselectivity in which the electron-rich arene was originally oxidized by iodine and followed by Cu-catalyzed arylation with another aromatic C−H bond.[12] Enlightened by that, we assume Pd^0/I_2 could be an ideal catalyst system to control the positional selectivity and yield of indole-3-carboxylate through two consecutive *in situ* steps: oxidation of indole to afford 3-iodoindole and its further carbonylation (Scheme 1, Path 4). Herein, we reveal this novel Pd-catalyzed oxidative carbonylation of indole with alcohol and phenol in the presence of iodine and K_2CO_3 under 1 atm of CO to form corresponding indole-3-carboxylates after the screening of reaction conditions (Supporting Information Table S1).

Scheme 1. Transformation of Free (NH)-Indole to Indole-3-carboxylate or Indole Carbamate



With the optimized conditions in hand, we next explored the substrate scope of the carbonylation of indole with alcohol (Scheme 2); the present $Pd(OAc)_2/I_2$ catalyst system showed good tolerance to the variation of indole substituents (**3a**−**3k**), giving indole-3-carboxylates with moderate to excellent yield. In general, indoles bearing an electron-donating group (methyl or methoxyl group) on the benzene ring (**3b**−**3e**) regardless of the position showed better reactivity compared with those bearing ester, cyano, or other electron-withdrawing groups (**3f**−**3k**), suggesting that the electron-donating substituent might facilitate the iodination step occurring on the C3-position of indole and then accelerate the following carbonylation. It is noteworthy that indoles with a halide (**3h**−**3k**) could smoothly undergo the reaction with the halide remaining, thus providing potential for further functionalizations. Additionally, alkyl

(6) (a) Guan, Z.-H.; Ren, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729. (b) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, *39*, 10442. (c) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312. (d) López, B.; Rodriguez, A.; Santos, D.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J. *Chem. Commun.* **2011**, *47*, 1054. (e) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222. (f) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (g) Du, Y.; Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 12074. (h) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326.

(7) (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (d) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.

(8) (a) Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A. *Nature* **1985**, *316*, 126. (b) Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C.-H.; Miche1, A. D.; Smith, W. L.; Wong, E. H. F. *J. Med. Chem.* **1993**, *36*, 2645.

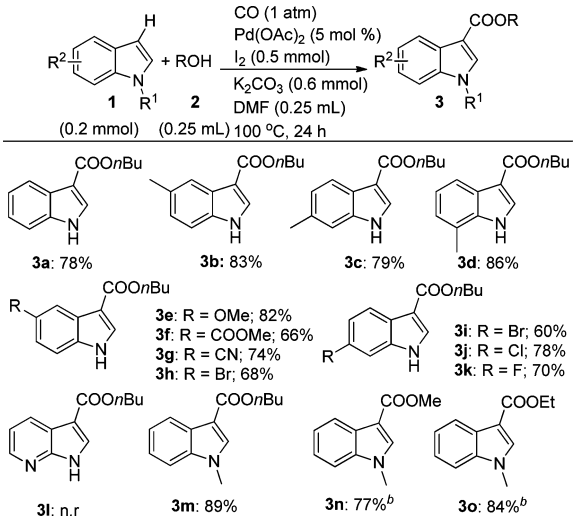
(9) Peterson, P. E.; Wolf, J. P., III; Niemann, C. *J. Org. Chem.* **1958**, *23*, 303.

(10) Zhang, H.; Liu, D.; Chen, C.; Liu, C.; Lei, A. *Chem.—Eur. J.* **2011**, *17*, 9581.

(11) Lang, R.; Wu, J. L.; Shi, L. J.; Xia, C. G.; Li, F. W. *Chem. Commun.* **2011**, *47*, 12553.

(12) (a) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2009**, *11*, 421. (b) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2010**, *12*, 2517. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577.

Scheme 2. Direct Carbonylation of Indole with Alcohol[a]

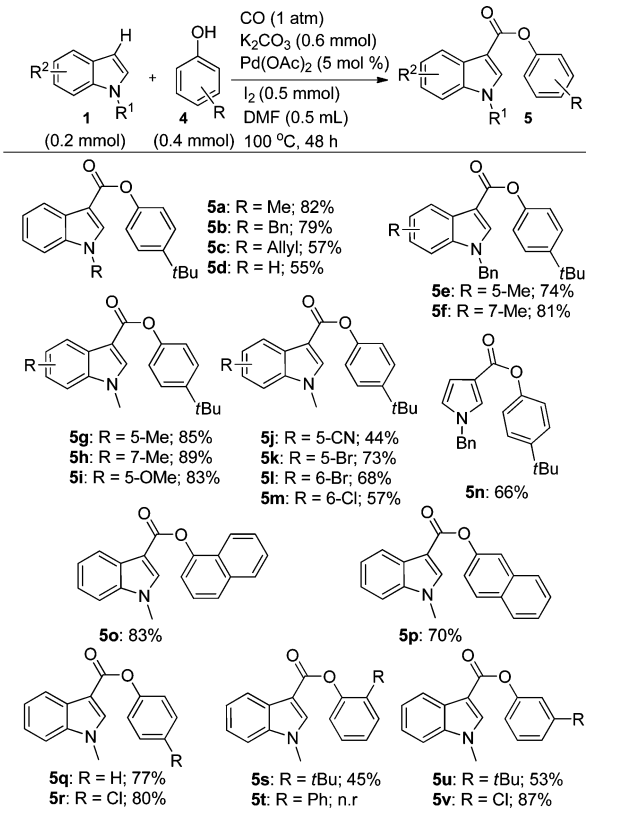


[a] Isolated yield. [b] 80 °C, 48 h.

indole-3-carboxylates were structurally confirmed by the X-ray crystal diffraction analysis of a representative product (**3h**, CCDC number 873074). The 7-azaindole with another nitrogen atom *meta* to the NH-group gave no reaction (**3l**), and the iodinated intermediate was also not observed. Compared with the reported Pd and Rh catalyst system, *N*-methylindole could furnish a higher yield of the corresponding carboxylate (**3m**, 89%) under the current catalytic system.[10,11] Gratifyingly, low-carbon aliphatic alcohols such as methanol and ethanol, which are not efficient nucleophilic alcohols in many other direct carbonylations,[5c,10,11] can readily be used affording high yields of the target products (**3n** and **3o**) under a lower reaction temperature.

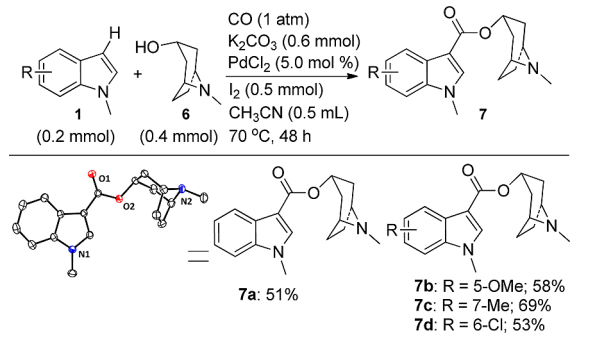
Unlike alcohol, phenol has been rarely utilized as a terminating nucleophile in the carbonylation to yield target ester;[13] however, its indole-3-carboxylate is indeed a privileged structure that could be found in many biologically active compounds, such as Herdmanines D (Figure 1, compound **2**), which demonstrated antibacterial activity in recent studies.[14] To the best of our knowledge, no one-step preparation of phenyl indole-3-carboxylate has ever been achieved. As summarized in Scheme 3, the present $Pd(OAc)_2/I_2$ catalyst system showed good generality toward the carbonylation of indole with an aromatic hydroxyl-nucleophile. Various *N*-substituted indoles could be readily carbonylated with phenols generating moderate to excellent yields of the desirable esters (**5a**–**5c**), and free (NH)-indole was also well tolerated (**5d**). As expected, *N*-substituted indoles with electron-giving groups on the benzene ring tend to furnish higher yields (**5e**–**5i**), and among them a representative structure of **5i** was verified by X-ray crystal diffraction analysis (CCDC number 873075). Furthermore, carbonylations of indoles having electron-withdrawing

Scheme 3. Direct Carbonylation of Indole with Phenol



functionalities proceeded smoothly in to provide moderate to good yields of **5j**–**5m**. Taking *N*-methylindole as an example, the electronic and steric effects of the aromatic hydroxyl-nucleophile were also investigated. Naphthol afforded good yields of target esters (**5o** and **5p**). The substituent on the *para*-position of the phenol would not significantly affect the reactivity; both phenol and 4-chloride phenol could go through the reaction (**5q** and **5r**). But the steric hindrance of the *ortho*-substituent drastically reduced the reactivity (**5s** and **5t**); phenol with a *tert*-butyl group on the *meta*-position (**5u**) was less active than that with chloride (**5v**), suggesting the electronic negativity of the –OH group also played an important role in the carbonylative reactivity.

Scheme 4. Direct Carbonylative Synthesis of Tropisetron



(13) Zeng, F.; Alper, H. *Org. Lett.* **2011**, *13*, 2868.
(14) Li, J. L.; Han, S. C.; Yoo, E. S.; Shin, S.; Hong, J.; Cui, Z.; Li, H.; Jung, J. H. *J. Nat. Prod.* **2011**, *74*, 1792 and references therein.

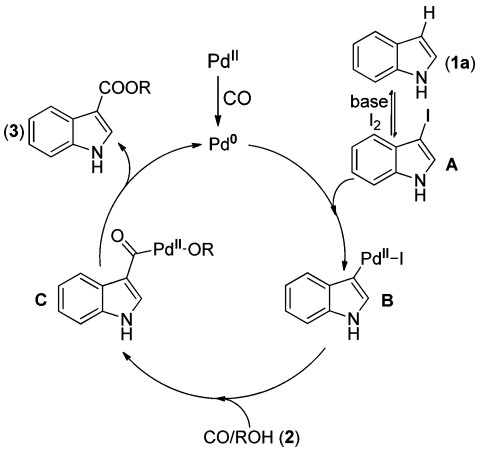
As mentioned above, tropisetron (**7**) is one kind of 5-HT_3 antagonist and now is in clinical use for the treatment of cancer chemotherapy-induced emesis. Its traditional synthetic method involved using indole-3-carboxylic acid chloride and a strong base such as *n*-butyl lithium through multistep reactions;[15] currently there is no direct way to synthesize tropisetron from simple indole and tropine (**6**) under mild conditions. Surprisingly, only a trace amount of tropisetron product (**7a**) was detected in the direct carbonylation of **1** with **6** under the above conditions, indicating that tropine showed an extremely different nucleophilic property in the present reaction compared with the previous alcohol and phenol. Finally, under the reoptimized conditions (Scheme 4), a 51% yield of **7a** was obtained, and other tropisetron analogues (**7b**–**7d**) could also be smoothly synthesized. Among the array of these bioactive compounds, a representative structure of **7a** was further confirmed by X-ray single crystal diffraction analysis (CCDC number 885831). For a comparison, the reported oxidative Pd- and Rh-catalyst systems were also applied to this direct synthesis of **7** but failed (Table S2 in Supporting Information). Therefore, the present Pd-catalyzed procedure may provide a more convenient way toward a vast expansion in the scope of valuable tropisetron analogues.

Based on the above experimental investigations and other related studies,[2,12,16] the excellent regioselectivity of the reaction could probably be elucidated by iodination and a further Pd^0-initiated carbonylation mechanism (Scheme 5). Taking 1*H*-indole (**1a**) for example, it is originally oxidized to 3-iodo-1*H*-indole (**A**), which could be detected by GC/MS analysis, and then a reactive Pd^0 species generated from CO reduction of Pd^{II} would preferentially initiate oxidative addition affording intermediate **B** rather than coordinate to the HN-position of **1a**, which usually lead to a carbamate or urea product. Subsequently, insertion of CO and alcohol yields the Pd^{II} acyl intermediate **C** that undergoes reductive elimination to release target product **3** and simultaneously regenerates the Pd^0 species.

(15) Langlois, M.; Soulier, J. L.; Yang, D.; Bremont, B.; Florac, C.; Rampillon, V.; Giudice, A. *Eur. J. Med. Chem.* **1993**, *28*, 869.

(16) (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673.

Scheme 5. A Plausible Catalytic Cycle



In conclusion, a novel strategy for the Pd-catalyzed direct carbonylation of various indoles to synthesize indole-3-carboxylates in moderate to excellent yields has been successfully developed. This methodology showed good generality to indole, alcohol, and/or phenol with high regioselectivity. Furthermore, the current catalytic procedure could be conveniently applied to the systematic synthesis of biologically active tropisetron from easily available starting materials. Further explorations on the mechanism and more synthetic applications of the present method are under investigation in our laboratory.

Acknowledgment. We gratefully acknowledge the Chinese Academy of Sciences and the National Natural Science Foundation of China (21002106, 21133011) for generous financial support.

Supporting Information Available. General experimental procedures, CIF information, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.