J|A|C|S COMMUNICATIONS

Published on Web 09/10/2010

Palladium-Catalyzed Intermolecular Decarboxylative Coupling of 2-Phenylbenzoic Acids with Alkynes via C−H and C−C Bond Activation

Congyang Wang,* Souvik Rakshit, and Frank Glorius*

Westfälische Wilhelms-Universität Münster, NRW Graduate School of Chemistry, Organisch-Chemisches Institut, Corrensstrasse 40, 48149 Münster, Germany

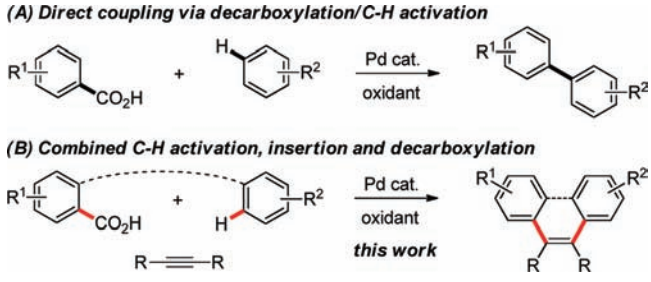
Received July 11, 2010; E-mail: wangcy@iccas.ac.cn; glorius@uni-muenster.de

Abstract: A novel protocol for palladium-catalyzed intermolecular formal [4 + 2] annulation of 2-phenylbenzoic acids with alkynes is described. Acridine is shown to be essential for the high reaction efficiency. Phenanthrene derivatives are formed in moderate to good yields without coupling (pseudo)halides or organometallic species.

Transition-metal catalyzed carbon−carbon bond formations have become powerful tools to construct organic molecules. Prefunctionalized substrates such as organohalides or pseudohalides and organometallic compounds are coupled in these transformations. Recently, the use of carbon-based leaving groups emerged as an attractive alternative defying the high dissociation energies (BDEs) of C−C bonds.[1] Among them, pioneering work from the groups of Myers, Goossen, Bilodeau, and others employing arene carboxylic acids as coupling partners represents a major breakthrough in this field.[2−4] A variety of benzoic acids could be coupled with aryl halides, triflates, diaryliodonium triflates, or tosylates via decarboxylative coupling affording biaryl compounds under properly tuned catalyst systems.[3]

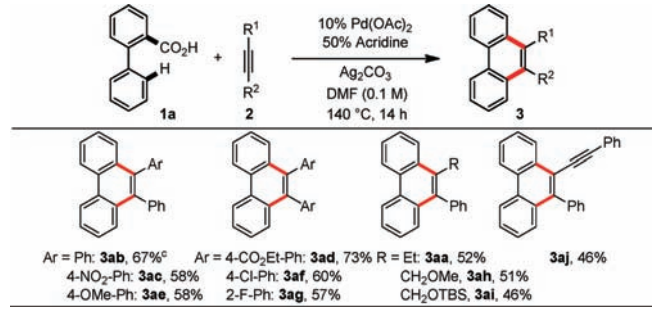
Subsequently, Crabtree et al., we, and others further extended the concept to the C−H activation field disclosing the direct aryl−aryl bond formation through a decarboxylation/C−H activation sequence (Scheme 1A).[5] The merging of two challenging areas created new attractive strategies for C−C bond formations since neither organohalides nor sensitive organometallics are required in these processes. Herein we report the palladium-catalyzed intermolecular formal [4 + 2] annulation of 2-phenylbenzoic acids with alkynes affording phenanthrenes (Scheme 1B).[6]

Scheme 1. Merging Decarboxylation and C−H Activation



To test our hypothesis, we first examined the reaction of 2-phenylbenzoic acid **1a** with 1-phenyl-1-butyne **2a** (Table 1). After extensive screening of a large array of reaction parameters,[7] we found that the addition of 0.5 equiv of pyridine derivatives played a pivotal role for the high efficiency of the desired reaction. This kind of beneficial effect of pyridine ligands in palladium-catalyzed reactions has recently been demonstrated by Stoltz et al. and Yu et al.[8] After surveying a variety of pyridine derivatives, the best results were obtained using acridine.[7] Finally, using 10 mol % $Pd(OAc)_2$, $AgCO_3$ as the oxidant in DMF, and 0.5 equiv of acridine provided optimal results.[7]

Table 1. Substrate Variation of Alkynes[a,b]



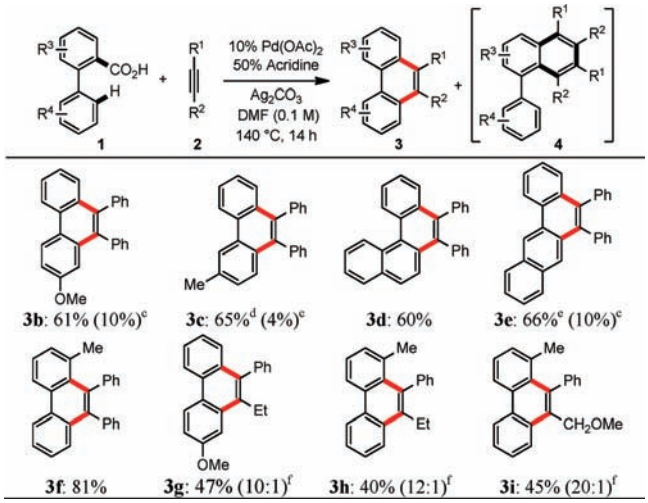
[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), acridine (0.25 mmol), Ag_2CO_3 (1.5 mmol), DMF (5 mL), 140 °C, 14 h. [b] Isolated yield. [c] Side product **4ab** isolated in 9% yield.

These conditions are compatible with a broad range of alkyne substrates (Table 1). Diphenylacetylene derivatives work well leading to the corresponding phenanthrenes **3ab**−**3ag** in good yields. Specifically, alkynes bearing electron-withdrawing nitro or ester groups or an electron-donating methoxy group are all successfully engaged in this reaction. It is noteworthy that halogen functionalities remain intact after reactions, thus offering handles for other valuable manipulations. Protected (OMe, OTBS) propargylic alcohols containing rather labile methylene groups are also applicable in this oxidative protocol (**3ah**, **3ai**). Only one C−C triple bond of buta-1,3-diyne was involved in the reaction leading to phenylethynyl substituted phenanthrene **3aj**. It should be noted that, in certain cases, very small amounts of coproducts **4** as mixtures of several regioisomers (see also Table 2) were detected but were not isolable (except for **4ab**).

Next, a variety of 2-phenylbenzoic acid derivatives were examined (Table 2). Substrates bearing different substitution patterns on the benzene ring undergoing C−H activation all led to the expected products **3b**, **3c** with the formation of **4b**, **4c** as minor products. Benzoic acids with a naphthyl moiety on the *ortho* positions afforded benzo[*c*]phenanthrene **3d** and benzo[*a*] anthracene **3e** under the same reaction conditions. Despite the enhanced steric hindrance, phenanthrene **3f** was obtained from the reaction of 2-phenyl-6-methyl benzoic acid **1f** and diphenylacetylene in high yield. Encouraged by these results, we sought to investigate the regioselectivity derived from the insertion of unsymmetrical alkynes. Gratifyingly, phenanthrenes **3g**−**3i** were formed as major isomers from the reactions of three different sets of substituted

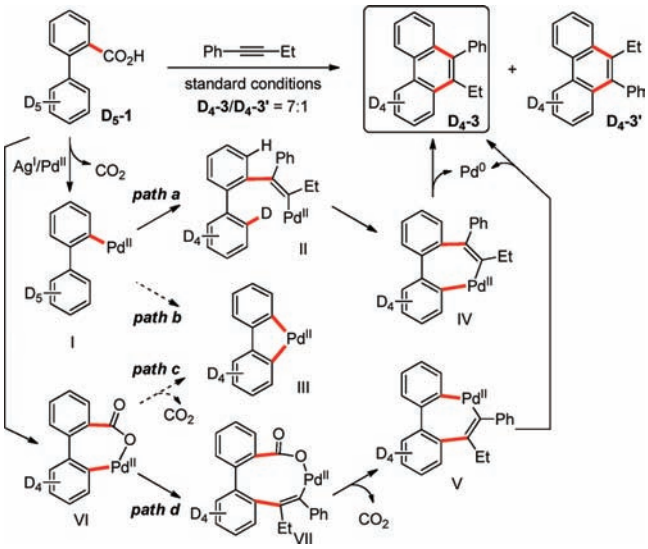
 10.1021/ja106130r

Table 2. Substrate Variation of 2-Phenylbenzoic Acids[a,b]



[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), acridine (0.25 mmol), Ag_2CO_3 (1.5 mmol), DMF (5 mL), 140 °C, 14 h. [b] Yield of the isolated, pure product. [c] The isolated yields of minor products **4** are listed in brackets. [d] Combined yield of two regioisomers **3c** and **3f** in the ratio of 2:1 (major isomer shown). [e] Combined yield of two regioisomers **3e** and **3e′** in the ratio of 1:1 (one isomer shown). [f] The ratio of two regioisomers are listed in brackets.

Scheme 2. Plausible Mechanism



benzoic acids and alkynes in high regioselectivities (≥10:1), which provided important insight into the mechanism of these reactions (vide infra).

Furthermore, two mechanistically insightful results were obtained. First, the reaction of $\mathbf{D_5}$**-1** with 1-phenyl-1-butyne **2a** provided products $\mathbf{D_4}$**-3**/$\mathbf{D_4}$**-3′** in a ratio of 7:1. Second, an intermolecular kinetic isotope effect (KIE) was determined to be 4.0,[7] rendering an electrophilic aromatic palladation for the C−H activation step unlikely.[9] These results are in agreement with two different mechanistic pathways (Scheme 2, *paths a* and *d*). Pd- or Ag-catalyzed (the latter one followed by transmetalation to Pd) decarboxylation of $\mathbf{D_5}$**-1** would afford metalated species **I**.[3,10] Two pathways might take place at this stage. One is the carbopalladation of alkyne to give vinylpalladium species **II**,[11] which then undergoes intramolecular C−D activation leading to palladacycle **IV** (*path a*), followed by reductive elimination. Alternatively, C−D activation in **I** would give palladacycle **III** (*path b*); however, this can be precluded because of its pseudosymmetrical nature, which is not in agreement with the obtained high levels of selectivity (7:1). Alternatively, carboxylic acid directed C−D activation might occur, providing **VI**. Whereas decarboxylation to **III** (*path c*) can be excluded (see above), the carbopalladation/decarboxylation/reductive elimination sequence (*path d*) is in agreement with the experimental observations.[11] Finally, Pd^0 is reoxidized to Pd^{II} by the Ag^I oxidant, thus closing the catalytic cycle (not shown).

In conclusion, we have developed the first palladium-catalyzed formal [4 + 2] annulation of 2-phenylbenzoic acids with alkynes via successive cleavage of both C−H and C−C bonds, obviating the need for organometallic and halide coupling partners. This methodology might find application in the synthesis of polycyclic aromatic hydrocarbons (PAHs) for material science.[12]

Acknowledgment. Generous financial support by the Alexander von Humboldt Foundation (C.W.) and the International NRW Graduate School of Chemistry (S.R.) is gratefully acknowledged. The research of F.G. was supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.

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

References

(1) For reviews on the coupling via C−C bond cleavage, see: (a) Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 778. (b) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022. (c) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (d) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (e) Nakao, Y.; Hiyama, T. *Pure Appl. Chem.* **2008**, *80*, 1097. (f) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300. (g) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2007**, *24*, 61. (h) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315.

(2) For an excellent review, see: Goossen, L. J.; Rodríguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100.

(3) For leading references in decarboxylative Heck reactions, see: (a) Tanaka, D.; Romeril, A. S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (b) For decarboxylative couplings of aromatic carboxylic acids, see: Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (c) Goossen, L. J.; Rodriguez, N.; Lange, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111. (d) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350. (e) Becht, J.-M.; Le Drian, C. *Org. Lett.* **2008**, *10*, 3161. For decarboxylative couplings of heteroaromatic carboxylic acids, see: (f) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (g) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674.

(4) For recent examples using carboxylic acids as *directing groups*, see: (a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (b) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (d) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295. (e) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478. (f) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7481.

(5) (a) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312. (b) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (c) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174. (d) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (e) Zhang, F.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768. (f) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564. (g) Zhou, J.; Hu, P.; Zhang, M.; Huang, S. J.; Wang, M.; Su, W. P. *Chem.—Eur. J.* **2010**, *16*, 5876.

(6) For representative syntheses of phenanthrene dervatives using organohalides or organometallic reagents, see: (a) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435. (b) Shimizu, M.; Nagao, I.; Tomioka, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 8096, and references therein.

(7) For more details, see Supporting Information.

(8) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072.

(9) For mechanistically insightful examples, see: (a) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128.

(10) (a) Goossen, L. J.; Linder, C.; Rodriguez, N.; Lange, P. P.; Fromm, A. *Chem. Commun.* **2009**, 7173. (b) Cornella, J.; Sanchez, C.; Banawa, D.;

Larrosa, I. *Chem. Commun.* **2009**, 7176. (c) Goossen, L. J.; Lange, P. P.; Rodríguez, N.; Linder, C. *Chem.—Eur. J.* **2010**, *16*, 3906.

(11) It is important to note that opposite carbopalladation regioselectivities were applied for pathways a and d, in order to account for the observed main product $\mathbf{D_4}$-**3**. Different levels of selectivity are reported for this kind of step: Unselective: (a) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. Selectivity required for path a: (b) Shi, Z.; Cui, Y.; Jiao, N. *Org. Lett.* **2010**, *12*, 2908. Selectivity required for path d: ref 10b. (c) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540. For Ni, see: (d) Liu, C.-C.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2010**, *12*, 3518. For Rh, see: (e) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585.

(12) Review: Wu, J.; Pisula, W.; Müllen, K. *Chem. Rev.* **2007**, *107*, 718.

JA106130R