ORGANIC LETTERS

2012
Vol. 14, No. 21
5452–5455

Palladium-Catalyzed C−H Functionalization Using Guanidine as a Directing Group: Ortho Arylation and Olefination of Arylguanidines

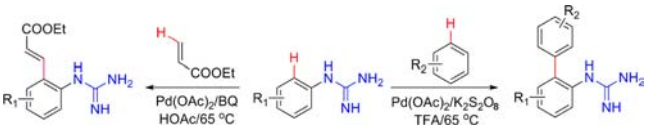
Jiaan Shao,[†] Wenteng Chen,[†] Marc A. Giulianotti,[‡] Richard A. Houghten,[‡] and Yongping Yu*[,†,‡]

Institute of Materia Medica, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, P. R. China and Torrey Pines Institute for Molecular Studies, 11350 SW Village Parkway, Port St Lucie, Florida 34987, United States

yyu@zju.edu.cn

Received September 13, 2012

ABSTRACT



Palladium-catalyzed C−H functionalization using guanidine as the directing group was achieved under mild reaction conditions. Various guanidine derivatives were produced in moderate to good yields by using simple unactivated arenes or ethyl acrylate as the source of arylation or olefination, respectively.

Palladium-catalyzed C−H bond functionalization for the C−C bond formation has emerged as a promising area in organic synthesis; however, it still remains a tremendous challenge.[1] In particular, the combination of palladium and directing groups provides an efficient way to facilitate C−H bond cleavage and transform a C−H bond to a C−C bond.[2]

In the past years, diverse directing groups, including pyridyl,[3a] carbamate,[3b] pyrazole,[3c] oxazolyl,[3d] amide,[3e] oxime ether,[3f] ketones,[3g] hydroxyl,[3h] and carboxylic acids,[3i,j] have been developed to assist aromatic C−H bond activation.

Guanidines are important structural motifs in a wide range of molecules with numerous applications such as histamine receptor agonists,[4] antidiabetic,[5] adrenoceptor antagonists,[6] as well as chiral catalysts.[7] Guanidines also have been widely used as coordination groups with various metals in many useful complexes.[8] However, to the best of our knowledge, using guanidine as the directing group to achieve C−H functionalization of substituted aromatics

[†] Zhejiang University.
[‡] Torrey Pines Institute for Molecular Studies.

(1) (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(2) (a) Wang, X. S.; Leow, D.; Yu, J. Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864. (b) Zhao, Y. S.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948. (c) Yu, M.; Xie, Y. G.; Zhang, Y. H. *Org. Lett.* **2012**, *14*, 2164. (d) Ji, X. C.; Huang, H. W.; Li, Y. B.; Chen, H. J.; Jiang, H. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1. (e) Li, D. D.; Yuan, T. T.; Wang, G. W. *ChemComm.* **2011**, *47*, 12789.

(3) (a) Desai, L. V.; Stower, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (b) Chao, F.; Loh, T. P. *ChemComm.* **2011**, *47*, 10458. (c) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146. (d) Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (e) Li, D. D.; Yuan, T. T.; Wang, G. W. *J. Org. Chem.* **2012**, *77*, 3341. (f) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C. H. *Chem.—Eur. J.* **2010**, *16*, 1436. (g) Kishor, P.; Jeganmohan, M. *Org. Lett.* **2011**, *13*, 6144. (h) Lu, Y.; Wang, D. H.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. (i) Wang, D. H.; Engle, K. M.; Shi, B. F.; Yu, J. Q. *Science* **2010**, *327*, 315. (j) Shi, B. F.; Zhang, Y. H.; Lam, J. K.; Wang, D. H.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 460.

(4) Igel, P.; Schneider, E.; Schnell, D.; Elz, S.; Seifert, R.; Buschauer, A. *J. Med. Chem.* **2009**, *52*, 2623.

(5) Coxon, G. D.; Furman, B. L.; Harvey, A. L.; McTavish, J.; Mooney, M. H.; Arastoo, M.; Kennedy, A. R.; Tettey, J. M.; Waigh, R. D. *J. Med. Chem.* **2009**, *52*, 3457.

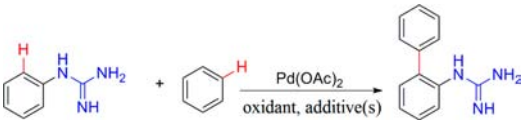
(6) Rodriguez, F.; Rozas, I.; Ortega, J. E.; Erdozain, A. M.; Meana, J. J.; Callado, L. F. *J. Med. Chem.* **2008**, *51*, 3304.

(7) Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc.* **2011**, *133*, 5695.

(8) (a) Singh, T.; Kishan, R.; Nethaji, M.; Thirupathi, N. *Inorg. Chem.* **2012**, *51*, 157. (b) England, J.; Farquha, E. R.; Guo, Y. S.; Cranswick, M. A.; Ray, K.; Münck, E.; Que, L., Jr *Inorg. Chem.* **2011**, *50*, 2885. (c) Tskhovrebov, A. G.; Bokach, N. A.; Haukka, M.; Kukushkin, V. Y. *Inorg. Chem.* **2009**, *48*, 8678.

10.1021/ol302533w
Published on Web 10/24/2012

Table 1. Screening of The Reaction Condition of Ortho-Arylation[a]



entry	oxidant (equiv)	additive (s)	yield (%)[b]
1	Ag_2CO_3 (2)	10 equiv of TFA	0
2	Ag_2O (2)	10 equiv of TFA	0
3	$Cu(OAc)_2$ (2)	10 equiv of TFA	0
4	p-benzoquinone (2)	10 equiv of TFA	trace
5	air	10 equiv of TFA	0
6	$K_2S_2O_8$ (2)	10 equiv of TFA	61
7	**$K_2S_2O_8$ (3)**	**10 equiv of TFA**	**72**
8	$K_2S_2O_8$ (4)	10 equiv of TFA	70
9	$K_2S_2O_8$ (3)	10 equiv of HOAc	0
10[c]	$K_2S_2O_8$ (3)	10 equiv of TFA	53
11[d]	$K_2S_2O_8$ (3)	10 equiv of TFA	66
12[e]	$K_2S_2O_8$ (3)	10 equiv of TFA	58

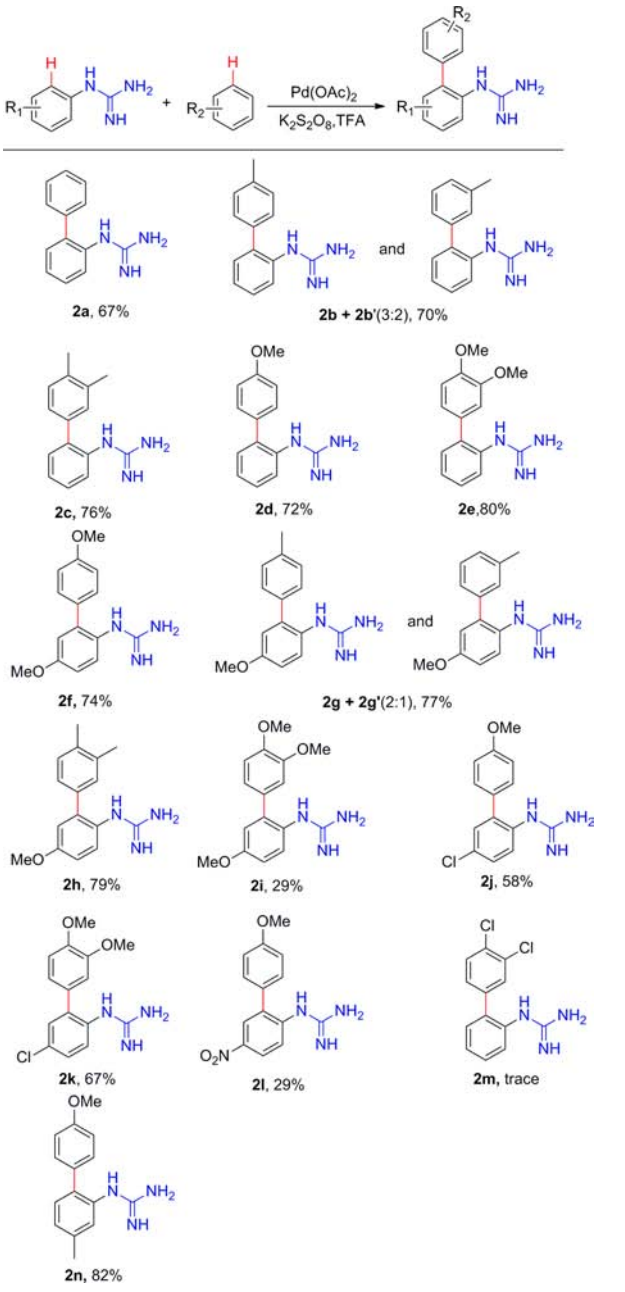
[a] Reaction conditions: phenyguanidine carbonate salt (0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), benzene (1 mL), TFA (5 mmol, 10 equiv), $K_2S_2O_8$, 65 °C, 48 h. The most successful entry is highlighted in bold. [b] Determined by high-performance liquid chromatography. [c] 5 mmol % $Pd(OAc)_2$ was used. [d] Reaction was performed at 80 °C for 48 h. [e] Reaction was performed at 65 °C for 36 h.

has not been explored in the literature. The important applications of guanidine derivatives in drug discovery and natural product synthesis prompted us to develop a Pd-catalyzed C−H functionalization of aryl guanidines.

The biaryl linkage is an important structural motif that is prevalent in numerous organic compounds, including natural products,[9a] pharmaceuticals,[9b] privileged ligands[9c] and conjugated materials.[9d] Palladium-catalyzed direct oxidative functionalization of C−H bonds of two arene coupling partners constitutes an important and desirable process for the synthesis of biaryls.[10] So the attempt using phenylguanidine as a test substrate to react with benzene under various conditions to form a C−C biaryl linkage was carried out as the primary case study. By surveying various reaction parameters, we obtained key results shown in Table 1.

First, the reaction was carried out by using $Pd(OAc)_2$ (10 mol %) as the catalyst in the presence of different oxidants with TFA. However, no conversation was observed at 65 °C for 48 h when Ag_2CO_3, Ag_2O or $Cu(OAc)_2$ were used as the oxidant (Table 1, entry 1, 2 and 3). There was also no conversion observed when the reaction was exposed to the air without any oxidant (Table 1, entry 5). A trace amount of the conversion occurred when BQ (*p*-benzoquinone) was used as the oxidant (Table 1, entry 4). To our delight, the conversion was improved significantly when BQ was replaced by potassium persulfate ($K_2S_2O_8$), and the ideal amount of $K_2S_2O_8$ was determined to be 3 equivelants to 1 equivalent of guanidine (Table 1, entry 4, 6−8). When the same reaction was carried out in the absence of $K_2S_2O_8$ or TFA, no desired product was observed. And if TFA was replaced by acetic acid, no desired product was observed

Scheme 1. Scope of The Orytho-Arylation Reaction[a]

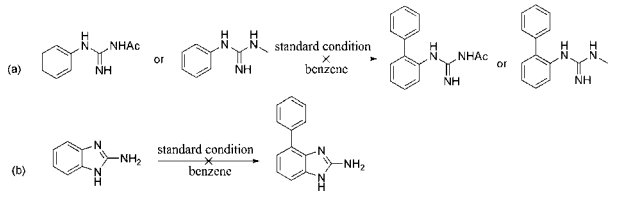


[a] Reaction conditions: guanidine carbonate salts (0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), arene (1 mL), TFA (5 mmol, 10 equiv), $K_2S_2O_8$(1.5 mmol, 1.0 equiv), 65 °C, 48 h. [b] Reaction was performed at 80 °C for 64 h. [c] The ratio of the regioisomers was detemined by ^1H NMR, products were isolated as their HCl saits, isolated yield.

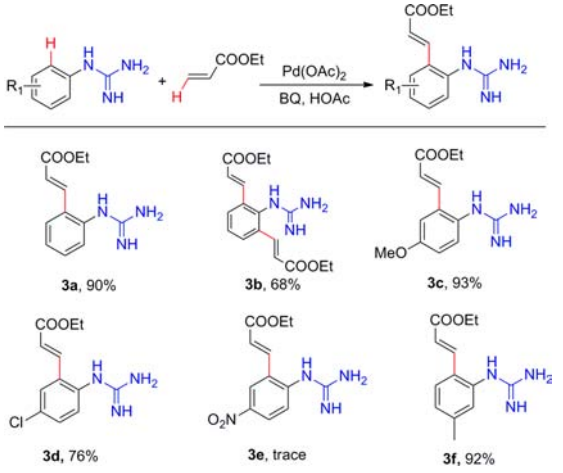
(9) (a) Baudoin, O.; Guéritte, F. *Stud. Nat. Prod. Chem.* **2003**, *29*, 355. (b) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135. (c) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. (d) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13326.

(10) (a) Zhao, X. D.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (b) Yu, M.; Dong, Z. J.; Wang, Y. Y.; Zhang, Y. H. *J. Org. Chem.* **2011**, *76*, 4987. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.***2007**, *129*, 11905. (d) Wang, X. S.; Leow, D. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864. (d) Lyons, T. W.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 4455. (e) Brasche, G.; Fortanet, J. G.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.

Scheme 2. Ortho-Arylation of Protected Phenylguanidine

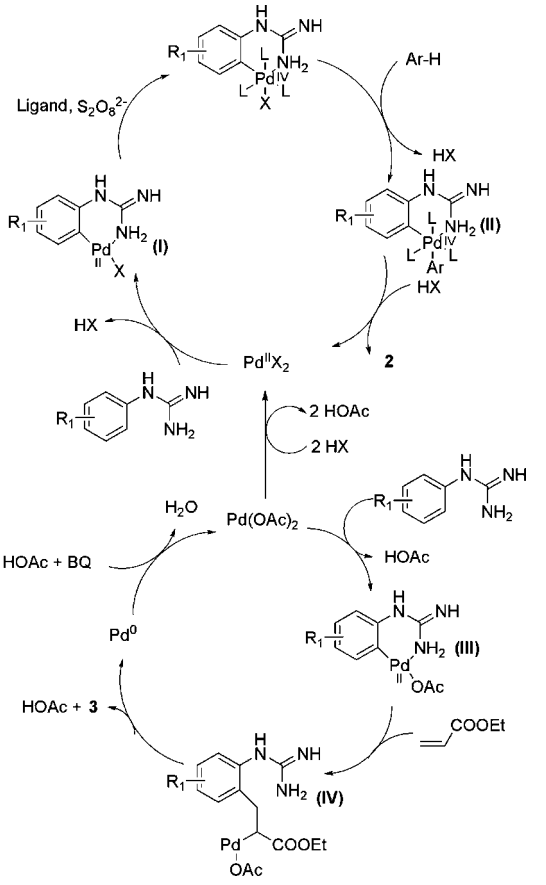


Scheme 3. Ortho-Olefination of Phenylguanidines with Ethyl Acrylate[a]



[a] Reaction conditions: guanidine carbonate salts (0.5 mmol, 1.0 equiv), ethyl acrylate (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (10 mol %), BQ (0.75 mmol, 1.5 equiv), HOAc (1.5 mL), 65 °C, 5 h, products were isolated as their HCl saits, isolated yield. [b] 2.5 equiv of ethyl acrylate was used, reaction was performed at 80 °C for 17 h [c] Reaction was performed at 80 °C for 24 h.

Scheme 4. Plausible Catalyic Mechanisms for the C−H Bond Activation



X=$OCOCF_3$

either (Table 1, entry 9). The results showed that both $K_2S_2O_8$ and TFA were required for the formation of the desired product. The reaction was also assessed at a higher temperature (Table 1, entry 11) but with a slight decrease in the yield. The amount of catalyst was also studied as well as the reaction time (Table 1, entry 10 and 12). On the basis of this initial study, the reaction was considered proceeding most efficiently when 3 equivalents of $K_2S_2O_8$, 10 mol % $Pd(OAc)_2$ were applied in the presence of TFA at 65 °C for 48 h.

With the optimized conditions in hand, we next examined the scope of the substrates as displayed in Scheme 1. Screening of arenes demonstrated that only electron-neutral or electron-rich arenes could take part in the arylation reaction efficiently. Electron-deficient arenes such as 1, 2-dichlorobenzene resulted in notably low conversion even under harsher reaction conditions (**2m**). Both electron-rich and electron-deficient phenylguanidines could be efficiently arylated using our protocol. However, the electron-rich phenylguanidines were more reactive, giving higher yields. Notably, most products were obtained as the monoarylated compounds as well as only one regioisomer. There were two regioisomeric products obtained when toluene was used as the arylation source (**2b**, **2b′** and **2g**, **2g′**). High regioselectivity was observed in the reaction of 1-m-tolylguanidine leading to arylation only at the C−H bond *para* to the methyl substituent presumably due to steric reasons (**2n**). However, if the guanidine group was protected by methyl or acetyl, there was no desired product observed under the standard reaction conditions. No desired product generated when 1H-benzo[d]imidazol-2-amine was applied under the standard conditions, either (Scheme 2).

In order to investigate the versatility of the guanidine directing group in C−H activation, we also explored the ortho-olefination reaction of substituted phenylguanidines with ethyl acrylate. After optimization of the reaction conditions, it was found that the olefination reaction could proceed successfully in the presence of $Pd(OAc)_2$ (10 mol %), and BQ (1.5 equiv) using acetic acid as the solvent at 65 °C for 5 h.

The optimized olefination reaction conditions were applied to additional substituted phenylguanidines (Scheme 3). Most of the substituted phenylguanidines reacted cleanly with ethyl acrylate to give the corresponding alkenylation products in moderate to good yields with excellent

E-stereoselectivity. The electron-rich phenylguanidines were more reactive giving higher yields. We also obtained the bis-substituted alkenylation products by adding additional one equivalent of ethyl acrylate while the reaction was performed at 80 °C for 17 h (**3b**).

It is known that acetoxylation and arylation of palladacycle in the presence of a strong oxidant were proposed to proceed via Pd^{IV}. A plausible mechanism for the catalytic arylation reaction is proposed as shown in Scheme 4. The proposed mechanism is based on previously reported chelation-assisted cross-couplings through C−H bond functionalization.[11] First, Pd^{II} coordinated with the nitrogen atom of the guanidine in the presence of TFA, which induced the formation of a cyclopalladated intermediate I by chelate-directed C−H activation. This Pd^{II} intermediate was oxidized by $K_2S_2O_8$ in the presence of arenes to afford a hexacoordinated Pd^{IV} intermediate II, which proceeded through a reductive elimination process to furnish the final ortho-arylation products and regenerate the Pd^{II} catalyst.

However, the ortho-olefination C−H bond functionalization seems more likely to follow a Pd^0/Pd^{II} pathway.[10b,12] Initially, the electronic attack of Pd^{II} into phenylguanidines formed the intermediate III, which inserted into olefins to afford the intermediate IV. The subsequent β-hydro elimination resulted in the product and liberates Pd^0 as well as acetic acid. The Pd^{II} was regenerated from the oxidation of Pd^0 by BQ.

In summary, we have successfully developed efficient palladium(II)-catalyzed methods for arylation and olefination of arenes by the use of guanidine as the directing group. The two different C−H functionalizations could be achieved by suitable control of the reaction condition.

Acknowledgment. This research was supported by the National Natural Science Foundation of China (81072516), Natural Science Foundation of Zhejiang Province (No. Z2110655) as well as the National Institute on Drug Abuse (DA031370) and the State of Florida, Executive Office of the Governor's Office of Tourism, Trade, and Economic Development.

Supporting Information Available. Experimental details, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (b) Wang, G. W.; Yuan, T. T.; Wu, X. L. *J. Org. Chem.* **2008**, *73*, 4717. (c) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (d) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488. (e) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. (f) Karthikeyan, J.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 9880. (g) Xu, L. M.; Li, B. J.; Yang, Z; Shi, Z. *J. Chem. Soc. Rev.* **2010**, *39*, 712. (h) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462.

(12) (a) Wang, L.; Guo, W.; Zhang, X. X.; Xia, X. D.; Xiao, W. J. *Org. Lett.* **2012**, *14*, 740. (b) Cai, G. X.; Li, Y. Z.; Wan, X. B.; Shi, Z. J. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (c) Lu, Y.; Wang, D. H.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. (d) Engle, K. M.; Wang, D. H.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137.