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# Palladium(II)-Catalyzed Oxidative Arylation of Quinoxalin-2(1*H*)-ones with Arylboronic Acids

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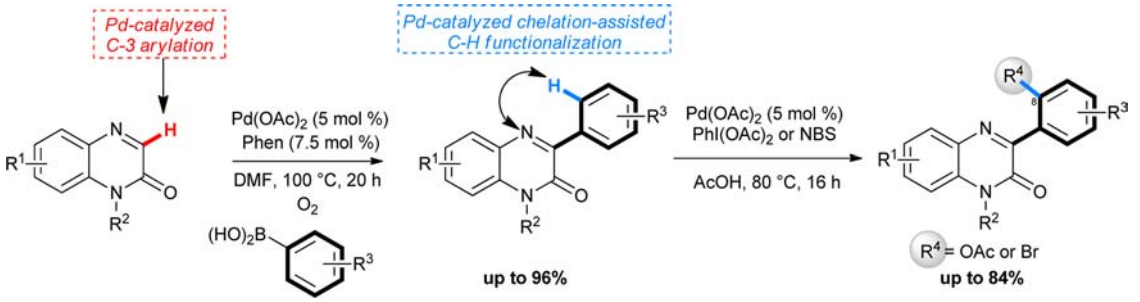
## ABSTRACT




**A straightforward palladium-catalyzed oxidative C-3 arylation of quinoxalin-2(1*H*)-ones with arylboronic acids is reported. This protocol is compatible with a wide range of functional groups and allows construction of various biologically important quinoxalin-2(1*H*)-one backbones.**

The transition-metal-catalyzed functionalization of nitrogen heterocycles[1] has emerged as an atom-economical alternative to the traditional processes for constructing heterocycle−aryl linkages, which constitute an important class of structures in natural and non-natural products. In contrast to the much more developed catalytic protocols for the arylation of electron-rich heteroarenes or those bearing a relatively acidic C−H bond, arylation of electron-deficient heterocycles has received much less attention.[2]

In connection with our ongoing program directed toward antagonists of the *N*-methyl-D-aspartate (NMDA) receptor,[3] we required the synthesis of 3-arylquinoxalin-2(1*H*)-ones **3** (Scheme 1). Traditional strategies to prepare such molecules involve the construction of the heterocycle rings by nontrivial and nonconvergent multistep reaction sequences[4] (Scheme 1, path a).

(1) (a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236–10254. (b) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826. (c) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (d) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902–4911. (e) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (f) You, S.-L.; Xia, J.-B. Palladium-Catalyzed Aryl−Aryl Bond Formation through Double C−H Activation. In *C−H Activation*; Yu, J.-Q., Shi, Z., Eds.; *Top. Curr. Chem.*; Springer: Berlin, 2010; Vol. 292, pp 165−194. (g) Messaoudi, S.; Brion, J.-B.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495–6516.

(2) Selected examples: (a) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2012**, *48*, 11769–11771. (b) Deb, A.; Manna, S.; Maji, A.; Dutta, U.; Maiti, D. *Eur. J. Org. Chem.* **2013**, 5208–5216. (c) Kim, D.; Ham, K.; Hong, S. *Org. Biomol. Chem.* **2012**, *10*, 7305–7312. (d) Khoobi, M.; Alipour, M.; Zarei, S.; Jafarpour, F.; Shafiee, A. *Chem. Commun.* **2012**, *48*, 2985–2987. (e) Li, Y.; Qi, Z.; Wang, H.; Fu, X.; Duan, C. *J. Org. Chem.* **2012**, *77*, 2053–2057. (f) Tiwari, V.-K.; Pawar, G.-G.; Das, R.; Adhikary, A.; Kapur, M. *Org. Lett.* **2013**, *15*, 3310–3313. (g) Zhao, H.; Wang, R.; Chen, P.; Gregg, B.-T.; Hsia, M.-M.; Zhang, W. *Org. Lett.* **2012**, *14*, 1872–1875. (h) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708–3709. (i) Kim, Y. W.; Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2012**, *77*, 9496–9503. (j) Molina, M. T.; Navarro, C.; Moreno, A.; Csaky, A. G. *Org. Lett.* **2009**, *11*, 4938–4941.

(3) Stawski, P.; Janovjak, H.; Trauner, D. *Bioorg. Med. Chem.* **2010**, *18*, 7759–7772.

(4) (a) Shaw, A. Y.; Denning, C. R.; Hulme, C. *Synthesis* **2013**, *45*, 459–462. (b) Křupková, S.; Funk, P.; Soural, M.; Hlaváč, J. *ACS Comb. Sci.* **2013**, *15*, 20–28. (c) Weïwer, M.; Spoonamore, J.; Wei, J.; Guichard, B.; Ross, N. T.; Masson, K.; Silkworth, W.; Dandapani, S.; Palmer, M.; Scherer, C. A.; Stern, A. M.; Schreiber, S. L.; Munoz, B. *ACS Med. Chem. Lett.* **2012**, *3*, 1034–1038. (d) Xu, Z.; Shaw, A. Y.; Dietrich, J.; Cappelli, A. P.; Nichol, G.; Hulme, C. *Mol. Diversity* **2012**, *16*, 73–79. (e) Carta, A.; Briguglio, I.; Piras, S.; Corona, P.; Boatto, G.; Nieddu, M.; Giunchedi, P.; Marongiu, M. E.; Giliberti, G.; Iuliano, F.; Blois, S.; Ibba, C.; Busonera, B.; La Colla, P. *Bioorg. Med. Chem.* **2011**, *19*, 7070–7084. (f) Dowlatabadi, R.; Khalaj, A.; Rahimian, S.; Montazeri, M.; Amini, M.; Shahverdi, A.; Mahjub, E. *Synth. Commun.* **2011**, *41*, 1650–1658. (g) Xue, Z.-Y.; Jiang, Y.; Peng, X.-Z.; Yuan, W.-C.; Zhang, X.-M. *Adv. Synth. Catal.* **2010**, *352*, 2132–2136.

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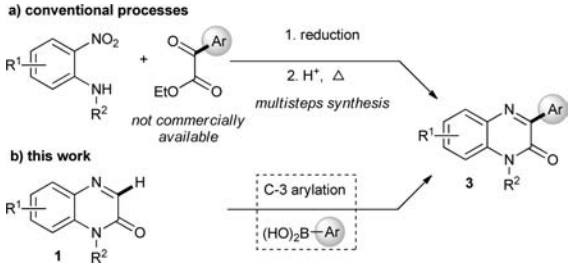
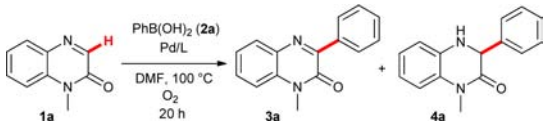
**Scheme 1**




Since the pioneering work of Suzuki and Miyaura,[5] the use of organoboron reagents as nucleophilic coupling partners with various organic electrophiles provides a powerful and general methodology for the formation of carbon−carbon[2,6] and carbon−heteroatom[6] bonds. As part of our continuing effort on the development of methods to functionalize heterocycles via transition-metal catalysis,[7] we report herein the C-3 arylation of quinoxalin-2(1*H*)-ones **1** with arylboronic acids using a catalytic amount of Pd(II) under oxygen atmosphere (Scheme 1, path b).

In our initial study, 1-*N*-methylquinoxalin-2(1*H*)-one **1a** and phenylboronic acid **2a** were chosen as model substrates for the C-3 arylation process (Table 1). The reaction was first investigated under Pd(II)-catalyzed conditions in the presence of phenanthroline as a ligand (7.5 mol %) and oxygen as an oxidant in DMF at 100 °C for 24 h. As summarized in Table 1, the screening conditions revealed that the source of palladium used has an important influence on the outcome of the present reaction. Thus, the use of $PdCl_2$ or $PdBr_2$ (5 mol %) did not promote the arylation reaction (entries 1 and 2), while in the presence of $Pd(OAc)_2$, the reaction led to a concomitant formation of the expected 3-phenyl quinoxalin-2(1*H*)-one **3a**, together with byproduct **4a** derived from the addition of phenylboronic acid to **1a** under Pd catalysis.[8] After a tedious separation, **3a** was isolated in a moderate 50% yield (entry 3). Attempts to avoid the formation of **4a** and increase the yield of **3a** have failed under various other palladium catalysts (entries 4 and 5). However, performing the reaction by bubbling oxygen for few a minutes (3 min) and leaving the $O_2$ balloon during the whole reaction time under otherwise identical conditions of entry 3 dramatically suppresses the formation of **4a** and increases the yield of **3a** up to 85% (entry 6). Evaluation of other ligands such as 5-nitrophenanthroline or 2,2′-bipyridine did not improve the conversion in **3a** (entries 7 and 8). Only 50% conversion was observed when the amount of the catalytic system was split in two (entry 9). In summary, the best selected conditions were found to require **1** (0.5 mmol), **2** (0.75 mmol), $Pd(OAc)_2$ (5 mol %), and phenanthroline (7.5 mol %) under a balloon of $O_2$ in DMF at 100 °C for 20 h. For control experiments, no conversion was observed in the absence of $Pd(OAc)_2$ or Phen and in the absence of $Pd(OAc)_2$ and Phen.[9]

**Table 1.** Optimization of **1a** Coupling with Phenylboronic Acid **2a**[a]




| entry | [Pd] | L | ratio **1a/3a/4a**[b] | yield (%)[c] |
|---|---|---|---|---|
| 1 | $PdCl_2$ | Phen | 100/0/0 | |
| 2 | $PdBr_2$ | Phen | 100/0/0 | |
| 3 | $Pd(OAc)_2$ | Phen | 10/60/30 | 50 |
| 4 | $Pd(TFA)_2$ | Phen | 35/5/60 | |
| 5 | $Pd(OPiv)_2$ | Phen | 20/60/25 | |
| **6**[d] | **$Pd(OAc)_2$** | **Phen** | **10/90/0** | **85**[f] |
| 7[d] | $Pd(OAc)_2$ | 5-$NO_2$Phen | 20/80/0 | |
| 8[d] | $Pd(OAc)_2$ | Bipy | 15/85/0 | |
| 9[d,e] | $Pd(OAc)_2$ | Phen | 50/50/0 | |

[a] Conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), Pd (5 mol %), ligand (7.5 mol %), DMF (2 mL) were heated in a sealed tube at 100 °C for 20 h under oxygen atmosphere. [b] The ratio was determined by $^1$H NMR in the crude reaction mixture based on the chemical shift of the proton signal of $-CH_3$ (ppm) at the N1 position (**1a**: $\delta$ = 3.70, **3a**: $\delta$ = 3.76, **4a**: $\delta$ = 3.42). [c] Yield of isolated **4a**. [d] Under $O_2$ balloon pressure for 20 h. [e] 2.5 mol % of $Pd(OAc)_2$ and 4 mol % of Phen were used. [f] No product could be formed in the absence of $Pd(OAc)_2$ and/or Phen.

Prompted by these results, we subsequently investigated the substrate scope for the Pd-catalyzed C-3 arylation of **1a** with a broad range of arylboronic acids. As illustrated in Scheme 2, electron-rich and electron-deficient, para- and meta-substituted arylboronic acids all underwent C-3 arylation of **1a** efficiently from moderate to good yields (products **3a**−**h** and **3k**). In the case of **3l**, the yield was moderate (40%) due to incomplete coupling reaction. The sterically demanding ortho-substitution pattern was tolerated toward coupling reaction of **1a**, leading to 3-arylquinoxalin-2(1*H*)-one derivatives including compound **3j** having a pyrene moiety. Interestingly, the presence of a

(5) (a) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723–6737. (b) For recent review, see: Johansson Seechurm, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.

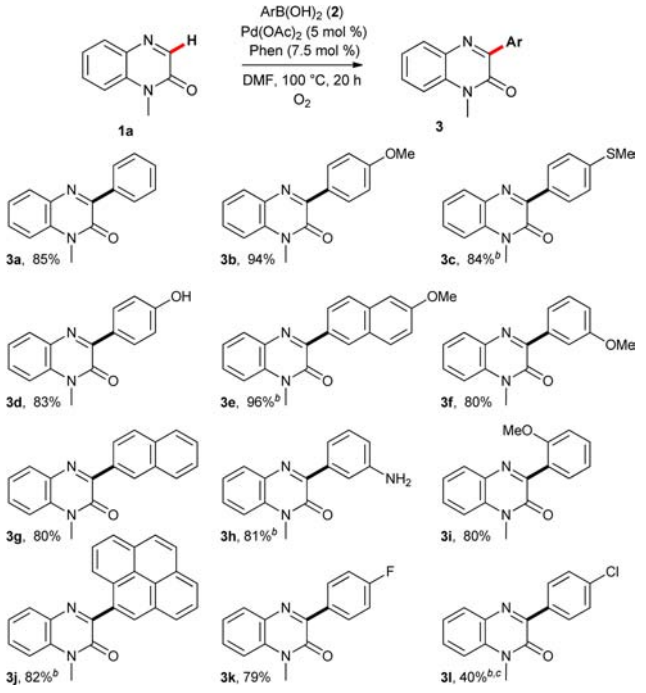
(6) For reviews see: (a) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829–856. (b) Rao, K. S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735–7754.

(7) (a) Sahnoun, S.; Messaoudi, S.; Peyrat, J.-F.; Brion, J. D.; Alami, M. *Tetrahedron Lett.* **2008**, *49*, 7279–7283. (b) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Org. Biomol. Chem.* **2009**, *7*, 4271–4278. (c) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6097–6102. (d) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *ChemCatChem* **2011**, *3*, 893–897. (e) Messaoudi, S.; Brion, J.-D.; Alami, M. *Org. Lett.* **2012**, *14*, 1496–1499. (f) Carrër, A.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Adv. Synth. Catal.* **2013**, *355*, 2044–2054.

(8) For Ru-catalyzed addition of arylboronates to aldimines, see: Park, Y. J.; Jo, E. A.; Jun, C. H. *Chem. Commun.* **2005**, 1185–1187.

(9) (a) Tohma, S.; Rikimaru, K.; Endo, A.; Shimamoto, K.; Kan, T.; Fukuyama, T. *Synthesis* **2004**, 909–917. (b) Zhao, L.; Liao, X.; Li, C.-J. *Synlett.* **2009**, 2953–2956. The C=N double bond of quinoxalin-2(1*H*)-one **1a** cannot be regarded as a simple imine function, as it is not reactive enough with phenylboronic acid under acidic conditions to furnish **3a**. As suggested by one of the referees, we checked the coupling of **1a** with **2a** using TFA in $CH_2Cl_2$ at room temperature (ref 7a). Under these conditions, the reaction was revealed to be ineffective and only starting material was recovered. In addition, performing the reaction of phenylboronic acid with **1a** or NH-free quinoxalin-2(1*H*)-one under Li's conditions (ref 7b), varying the reaction temperature (80−120 °C) as well as reaction time (2−24 h), did not provide any arylated compounds and only the starting material was recovered.

**Scheme 2.** Scope of Boronic Acid Coupling with Quinoxalin-2(1*H*)-one **1a**[a]




[a] Conditions: quinoxalinone **1a** (0.5 mmol), boronic acid 2 (1.5 equiv), Pd(OAc)2 (5 mol %), Phen (7.5 mol %), and DMF (2 mL) under $O_2$ (balloon pressure) at 100 °C for 20 h. [b] 2 equiv of arylboronic acid was used. [c] 52% of starting material **1a** was recovered unchanged.

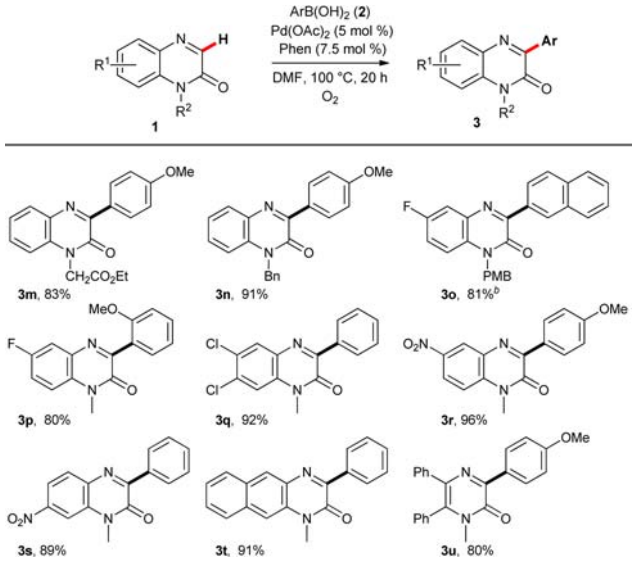
hydroxyl and free amino groups on the arylboronic acid partner did not interfere with the outcome of the present reaction (compounds **3d** and **3h**).

To expand the scope of our method further, a series of quinoxalin-2(1*H*)-ones as well as related heterocycles (e.g., pyrazin-2(1*H*)-one and benzo[*g*]quinoxalin-2(1*H*)-one) were subjected to the coupling protocol with various arylboronic acids (Scheme 3). We were pleased to observe that *N*-alkyl- and *N*-benzylquinoxalin-2(1*H*)-ones having electron-withdrawing or electron-donating groups on the aromatic nucleus led to the corresponding compounds **3m**−**s** in good yields. Interestingly, the reaction is not effective with tautomerizable[10] quinoxalin-2(1*H*)-one in which the nitrogen atom is unsubstituted, probably due to the very poor solubility of the substrate. Compounds **3q**−**s** bearing electrophilic functional groups are of particular interest, as they contain reactive handles and, as such, could be used as a foundation for the synthesis of more complex molecules. Finally, the use of this protocol to 5,6-disubstituted pyrazin-2(1*H*)-one as well as benzo-[*g*]quinoxalin-2(1*H*)-one was successful and provided the arylated compounds **3t**,**u** in 91 and 80% yields, respectively.

With substantial amounts of **3a** and **3b** in hand (Scheme 2), we focused our attention on demonstrating whether our method could be employed as a platform for

(10) Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300–11302.

**Scheme 3.** Scope of Quinoxalin-2(1*H*)-one **1** Coupling with Boronic Acids[a]




[a] Conditions: quinoxalinone **1** (0.5 mmol), boronic acid **2** (1.5 or 2 equiv), Pd(OAc)2 (5 mol %), Phen (7.5 mol %), DMF (2 mL) under $O_2$ (balloon pressure) at 100 °C for 20 h. [b] 2 equiv of boronic acid was used.

molecular diversity. We have been particularly interested in the regioselective C−H functionalization of substrates of type **3** using the nitrogen atom (N4) of the quinoxalin-2(1*H*)-one nucleus as the Lewis basic directing group. In this context, transition-metal-catalyzed chelation-assisted C−H functionalization has emerged as a powerful tool for the regioselective construction of carbon−carbon and carbon−heteroatom bonds.[11] Notably, 3-arylquinoxalin-2(1*H*)-ones **3v**−**x** bearing an acetate group[11d] or a bromine atom[11i,j] could easily be prepared via a regioselective Pd-catalyzed chelation-assisted C−H functionalization (Scheme 4).

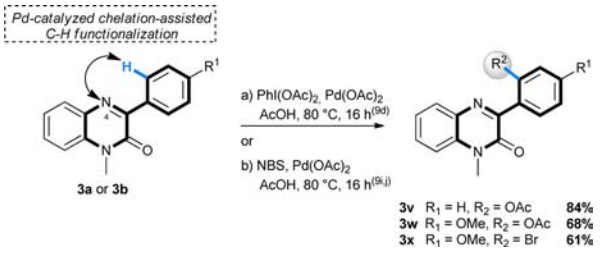
A possible mechanism for the C-3 arylation of quinoxalin-2(1*H*)-ones is depicted in Scheme 5. Arylpalladium complex **I**, which is formed in situ by the transmetalation of an aryl group from boron to palladium,[12] is envisioned

(11) For reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. Selected article: (b) Sanhueza, I. A.; Wagner, A. M.; Sanford, M. S.; Schoenebeck, F. *Chem. Sci.* **2013**, *4*, 2767–2775. (c) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936–946. (d) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149–4152. (e) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3286–3486. (f) Phani Kumar, N. Y.; Jeyachandran, R.; Ackermann, L. *J. Org. Chem.* **2013**, *78*, 4145–4152. (g) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332–3335. (h) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342–9345. (i) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483–11498. (j) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523–2526. (k) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11400–11404.

(12) (a) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2571–2573. (b) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709–1712.

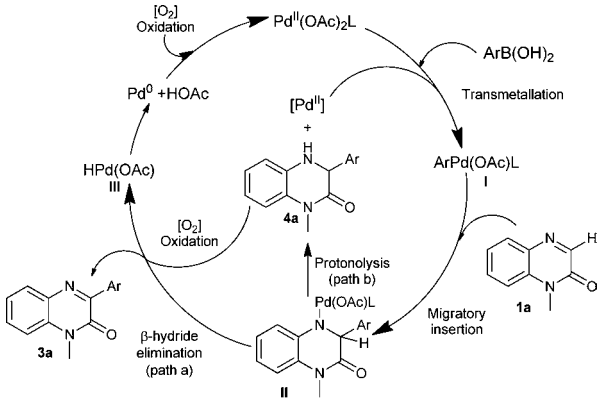
(13) (a) Ishiyama, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 12043–12044. (b) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2694–2695. (c) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356–15357.

**Scheme 4.** Regioselective Pd-Catalyzed Chelation-Assisted C−H Functionalization of **3a**,**b**



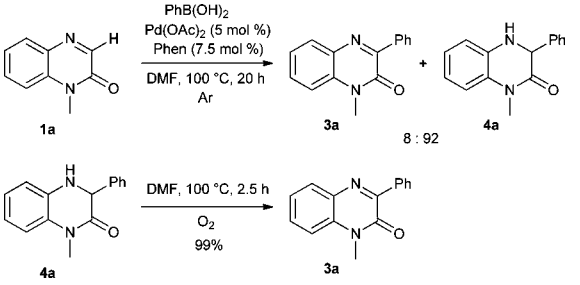

to take place as an initial step. This later evolves through the migratory insertion mechanism into quinoxalin-2(1*H*)-one **1a** to give a palladium(II) complex **II**.[9,13] Subsequent *β*-hydrogen elimination from **II** produces a Heck-type product **3a** and hydridopalladium(II) acetate **III** (path a). Compound **3a** could also be formed through oxygen-promoted oxidation of **4a** which arises from protonolysis of **II** (path b).

**Scheme 5.** Plausible Catalytic Cycle for the C-3 Arylation of Quinoxalin-2(1*H*)-ones




To gain insight into this reaction, we conducted the following experiments (Scheme 6). First, we studied the transformation in the absence of $O_2$. If the reaction involves a *β*-hydride elimination step from **II** (path a), theoretically the C-3 arylation of **1a** to furnish **3a** is expected to be difficult because the Pd(II) species cannot be regenerated from Pd(0). It was observed that the reaction of **1a** with **2a** under optimal conditions of entry 6 (Table 1) but using an argon atmosphere instead of

**Scheme 6**




oxygen furnished a mixture of **3a** and **4a** in a 8/92 ratio (Scheme 6). This result clearly suggests that **4a** is the reaction product which is oxidized into **3a** off the catalytic cycle. To further strengthen the above hypothesis, submitting the isolated compound **4a** to aerobic conditions (DMF, $O_2$, 100 °C) furnished the oxidized product **3a** quantitatively within only 2.5 h. Summarizing all the information, we assume that pathway b involving a protonolysis followed by oxidation of **4a** might be considered more likely, while the *β*-hydrogen elimination (path a) cannot be discarded.

In conclusion, we successfully developed an efficient and practical $Pd(OAc)_2$/phenanthroline-catalyzed system for C−H arylation of various quinoxalin-2(1*H*)-ones with arylboronic acids. The protocol exhibited a broad substrate scope with respect to both the coupling partners, thus providing an attractive alternative to the existing methods for the synthesis of 3-arylquinoxalin-2(1*H*)-ones **3** of biological interest. Moreover, we have demonstrated that the nitrogen atom of the quinoxalinone nucleus can be used in a regioselective Pd-catalyzed chelation-assisted C−H functionalization of 3-arylquinoxalin-2(1*H*)-ones **3**.

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**Supporting Information Available.** Experimental procedures and spectroscopic data 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.