

ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

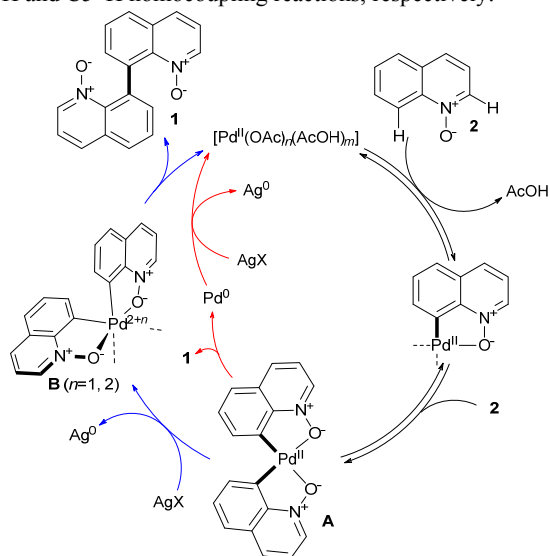
Communication

Experimental and Mechanistic Analysis of the Palladium-Catalyzed Oxidative C8-Selective C–H Homocoupling of Quinoline *N*-OxidesDavid E. Stephens,^a Johant Lakey-Beitia,^{a,b,c} Gabriel Chavez,^a Carla Ilie,^a Hadi D. Arman,^a and Oleg V. Larionov^{*a}⁵ Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A novel site-selective palladium-catalyzed oxidative C8–H homocoupling reaction of quinoline *N*-oxides has been developed. The reaction affords substituted 8,8'-biquinolyl *N,N'*-dioxides that can be readily converted to a variety of functionalized 8,8'-biquinolyls. Mechanistic studies point to the crucial role of the oxidant and a non-innocent behavior of acetic acid as a solvent.

Heteroaryl-heteroaryl bond formation is an important synthetic strategy en route to homo- and heterodimeric structural motifs with applications in catalysis,¹ drug discovery² and materials science.³ Catalytic oxidative C–H homocoupling of heteroarenes is an attractive method of direct biheteroaryl synthesis, as it bypasses prefunctionalization of the heteroarene precursors (e.g. as halides, stannanes or boronic acids). Recent examples of regioselective catalytic oxidative C–H homocoupling of heteroarenes include thiophenes (C2⁴/C3⁵), indoles (C2,^{5,6} C2/C3⁷), indolizines (C3),⁸ azoles (C2),⁹ and furans (C2).^{4c} In addition, pyridine and 1,2,3-triazole *N*-oxides undergo oxidative C2–H and C5–H homocoupling reactions, respectively.¹⁰



Scheme 1. Plausible mechanistic pathways for the oxidative C8–H homocoupling of quinoline *N*-oxides.

We have recently developed a regioselective Pd-catalyzed C8–H arylation of quinoline *N*-oxides.^{11,12} Kinetic and DFT computational studies point to the important role of acetic acid as a non-innocent solvent/ligand that directs the turnover-limiting cyclopalladation to the C8 position. It was later observed that

certain conditions favor formation of homodimer **1** as a minor by-product (<10% yield), that was hypothesized to be formed by the oxidative C–H homocoupling (Scheme 1). From the synthetic perspective, 8,8'-biquinolyl is a structurally important framework that has been successfully employed in the design of chiral ligands, as shown by Blackmore and co-workers,¹³ and is a key structural element of dimeric aporphinoid alkaloids.¹⁴ Mechanistically, Pd-catalyzed oxidative C–H homocoupling reactions remain poorly understood: while a Pd^{II}/Pd⁰ catalytic cycle has generally been postulated,⁵ mechanistic evidence suggests that in some cases higher oxidation state Pd species (e.g. a Pd^{IV}/Pd^{II} cycle)¹⁵ can be operative. This paper reports the development and a preliminary mechanistic study of the oxidative C8–H homocoupling of quinoline *N*-oxides.

Table 1. Oxidative C–H homocoupling of quinoline *N*-oxide (**2**).^a

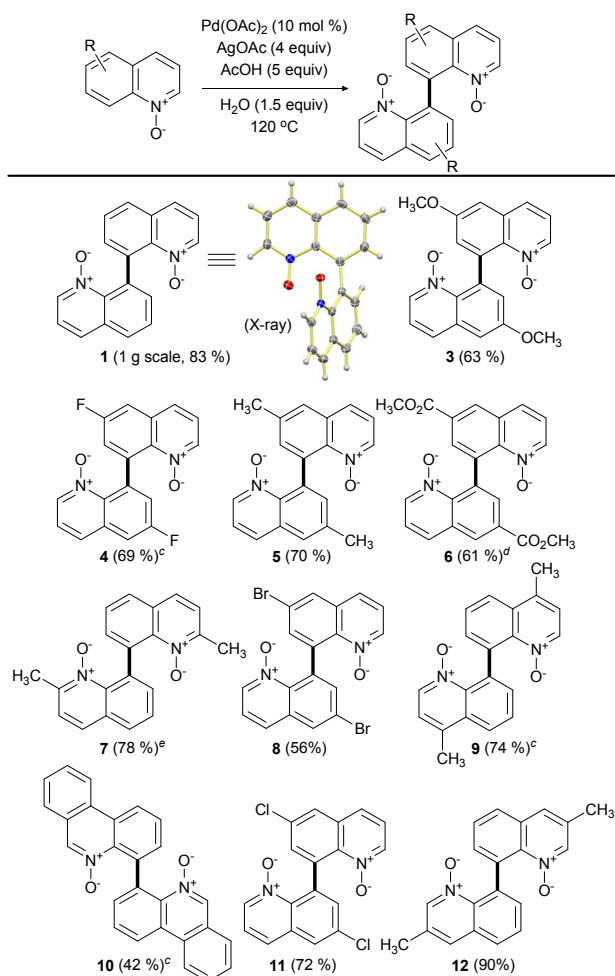
| Entry | Catalyst | Solvent (equiv.) | Oxidant (equiv.) | Yield (%) ^b |
|-----------------|---|---------------------------------|---------------------------------------|------------------------|
| 1 | Pd(OAc) ₂ | AcOH (30) | AgOAc (3) | 44 |
| 2 | Pd(O ₂ CCF ₃) ₂ | AcOH (30) | Ag ₃ PO ₄ (0.5) | 32 |
| 3 | PdCl ₂ | AcOH (30) | Ag ₃ PO ₄ (0.5) | 3 |
| 4 | Pd(OAc) ₂ | AcOH (30)/H ₂ O (5) | Oxone (2) | 12 |
| 5 | Pd(OAc) ₂ | AcOH (30)/H ₂ O (5) | Cu(OAc) ₂ (2) | 0 |
| 6 | Pd(OAc) ₂ | AcOH (15)/H ₂ O (5) | Ag ₃ PO ₄ (2) | 64 |
| 7 | Pd(OAc) ₂ | AcOH (30)/H ₂ O (15) | AgOAc (3) | 66 |
| 8 | Pd(OAc) ₂ | AcOH (15)/H ₂ O (5) | AgOAc (2) | 61 |
| 9 | Pd(OAc) ₂ | AcOH (15)/H ₂ O (5) | AgOAc (4) | 57 |
| 10 ^c | Pd(OAc) ₂ | AcOH (5)/H ₂ O (1.5) | AgOAc (4) | 82 |

^a Reaction conditions: **2** (0.2 mmol), catalyst (10 mol %), oxidant for 12 h at 120 °C. ^b Yields were determined by ¹H NMR analysis with 1,4-dimethoxybenzene as an internal standard added prior to work-up. ^c The reaction was carried out on 3.45 mmol scale.

Initial experiments showed that Pd(OAc)₂ was superior to other Pd catalysts (Table 1, entries 1–3), and that silver acetate and silver phosphate can both serve as efficient oxidants for the formation of biquinolyl **1**. Other oxidants, e.g. Cu(II) salts, Oxone, PhI(OAc)₂, led to low conversions (0–15%). The homocoupling was not observed in other solvents (e.g. *N,N*-dimethylformamide, *tert*-butanol, 1,2-dichloroethane, dioxane) confirming the crucial role of acetic acid in the cyclopalladation. Based on our earlier observation of the accelerating effect of water on C8–H arylation of substrate **2**,¹¹ reactions were carried out in the acetic acid/water system, and a 57–66% conversion

was achieved with a 2–3 : 1 molar ratio of AcOH/H₂O (entries 6–9, Table 1).

Table 2. Scope of the oxidative C8–H homocoupling reaction.^{a,b}



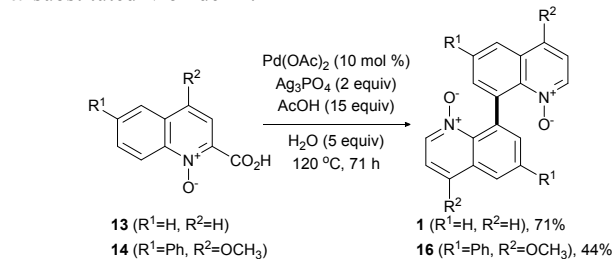
^a Reaction conditions: *N*-oxide (0.50 mmol), Pd(OAc)₂ (10 mol %), AgOAc (4 equiv), AcOH (5 equiv), H₂O (1.5 equiv), 120 °C, 12–24 h. ^b The yields are reported for isolated 8,8'-biquinolylium *N,N'*-dioxides. ^c 15 equiv AcOH and 5 equiv H₂O was used. ^d 20 mol % Pd(OAc)₂ was used. ^e The reaction was carried out with Ag₃PO₄ (2 equiv.), AcOH (15 equiv), and H₂O (5 equiv).

The conversion was further improved by reducing the amounts of acetic acid and water to 5 and 1.5 equiv, respectively, as a consequence of the increased effective concentrations of the reactants (entry 10). The C–H homocoupling was successfully

carried out on a 1 g scale and afforded product **1** in an 83% yield. The reaction can be carried out in the atmosphere of air that has no effect on the conversion. The C8/C2 selectivity is estimated to be >30:1, as no formation of C2–C2 or C2–C8 regioisomers was observed by ¹H NMR spectroscopy. The reaction exhibits a broad

scope and tolerates a variety of substituents in the quinoline core (Table 2). Halogens, including Br, are well tolerated, and benzylic C–H bonds remain unaffected. 4,7-Dichloroquinoline *N*-oxide did not undergo the C8-dimerization, indicating that C7-substituents may be detrimental to the reaction.

substrate for the homocoupling is quinoline *N*-oxide. The facile Ag-catalyzed decarboxylation may be due to the stabilization of the transition state by the electron-withdrawing N–O moiety, as it has been recently rationalized for ortho-substituted benzoic acids.¹⁶ The tandem C2-decarboxylation/C8–H homocoupling process was successfully expanded to the readily available

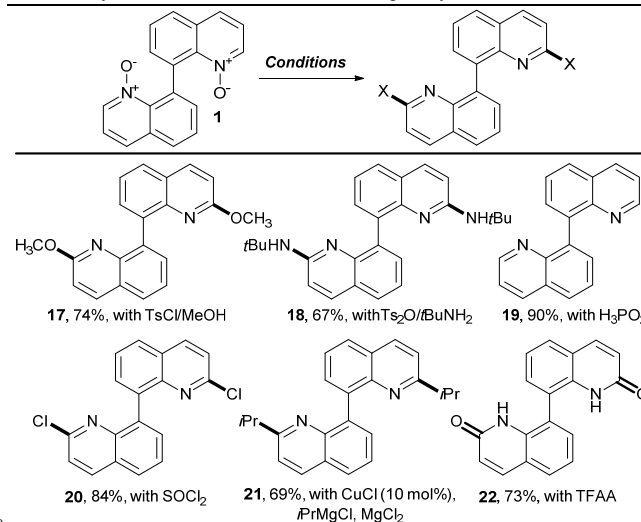


Scheme 2. Tandem C2-decarboxylation/C8–H homocoupling reaction of substituted 2-carboxyquinoline *N*-oxides.

As a corollary, the C8–H arylation of substrate **13** was carried out, and the corresponding cross-coupling product **15** was obtained in an 87% yield. This result compliments Hoarau's Ag- and Cu-mediated, Pd/phosphine-catalyzed C2-selective arylation of 2-carboxyquinoline *N*-oxides.¹⁷

The *N*-oxide moiety in the homocoupling products can be transformed into a number of functional groups in the C2-position (Table 3). For example, methoxy¹⁸ and *N*-*tert*-butylamino groups¹⁹ were installed in the 2 and 2'-positions in 74% (**17**) and 67% (**18**) yields, respectively.

Table 3. Synthesis of 2,2'-substituted 8,8'-biquinolylium *N,N'*-dioxides.



Similarly, a deoxygenation with hypophosphorous acid furnished 8,8'-biquinolylium (**19**), whereas a reaction with thionyl chloride²⁰ afforded 2,2'-dichloro-8,8'-biquinolylium (**20**) in an 84% yield. In addition, 2,2'-dialkyl-8,8'-biquinolylium **21** was readily obtained by a copper-catalyzed reaction with a Grignard reagent,²¹ and 8,8'-biquinolone **22** was formed by a trifluoroacetic anhydride-

mediated rearrangement.²² A reaction of **2** with $\text{CF}_3\text{Si}(\text{CH}_3)_3$ in the presence of potassium *tert*-butoxide²³ unexpectedly led to a nearly quantitative conversion to 8,8'-biquinolyl (**19**) presumably due to the increased steric encumbrance in the dimeric *N*-oxide.

The mechanism of the homocoupling reaction was briefly examined by means of kinetic isotope effect and Hammett plot studies. We previously determined by means of H/D-exchange experiments that a highly C8-selective (>30:1) cyclopalladation of **1** occurs in the $\text{Pd}(\text{OAc})_2/\text{AcOH}$ system.

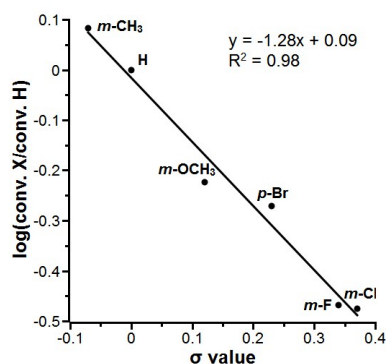
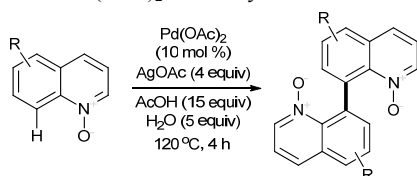


Figure 1. Hammett plot for the oxidative C8–H homocoupling of quinoline *N*-oxide.

It was further determined, that the cyclopalladation was a reversible and turnover-limiting step. It was therefore of interest to compare the mechanistic data for C8–H homocoupling with those for the C8–H arylation. Primary KIE was measured in parallel experiments with substrate **2** in $\text{CH}_3\text{CO}_2\text{H}/\text{H}_2\text{O}$, and 2,8-*d*₂-**2** in $\text{CD}_3\text{CO}_2\text{D}/\text{D}_2\text{O}$, respectively. It was determined that the homocoupling proceeded with no primary KIE ($k_{\text{H}}/k_{\text{D}} = 1$), in contrast to the arylation ($k_{\text{H}}/k_{\text{D}} = 2$), indicating that the cyclopalladation was not a turnover-limiting step in this case. This result was further supported by the Hammett study (Figure 1) that provided a ρ value of -1.28 for the homocoupling. This ρ value is substantially lower than that observed for the $\text{Pd}(\text{OAc})_2$ -catalyzed C8–H/D exchange for **2** in AcOH ($\rho = -2.98$). Furthermore, since no palladacyclic intermediates were isolated or observed by ¹H NMR, and the reaction afforded exclusively homocoupling products (e.g. C8–C8 and not C8–C2), the second cyclopalladation step is likely reversible in AcOH under the reaction conditions, and is mechanistically similar to the first cyclopalladation step.^{15,24} Hence, the combined KIE, Hammett²⁵ and kinetic results are more consistent with the reductive elimination as a turnover-limiting step of the reaction. Further, experiments with varied amounts of $\text{Pd}(\text{OAc})_2$ in the absence of AgOAc indicate that the reaction does not proceed through a $\text{Pd}^{\text{II}}/\text{Pd}^0$ catalytic cycle, as no correlation was observed between the concentration of $\text{Pd}(\text{OAc})_2$ and conversion of **2**.²⁶ This result suggests that the oxidation state of palladium that is required for the reductive elimination en route to **1** cannot be accessed in the absence of the Ag^I oxidant,²⁷ pointing to higher oxidation state pathways as likely mechanistic alternatives.

In conclusion, we have developed a new C8-selective C–H homocoupling of quinoline *N*-oxides. The reaction proceeds with a high degree of site-selectivity to give 8,8'-biquinolyl *N,N'*-dioxides that can serve as precursors to a number of 2,2'-substituted 8,8'-biquinolyls. Preliminary mechanistic analysis points to involvement of the higher oxidation state Pd and the crucial role of acetic acid for the C8-regioselectivity.

Financial support by the Welch Foundation (AX-1788), NIGMS (SC3GM105579), the Voelcker Fund and UTSA is gratefully acknowledged. JLB is supported by the Institute for Training and Development of Human Resources (IFARHU), National Secretariat for Science, Technology and Innovation (SENACYT), and Ministry of Economic and Finance (DIPRENA-DPIP-10866-2013) of Panama. Mass spectroscopic analysis was supported by a grant from NIMHD (G12MD007591).

Notes and references

- ^a Department of Chemistry, University of Texas at San Antonio, San Antonio, TX 78249, United States. E-mail: oleg.larionov@utsa.edu
- ^b Centre for Biodiversity and Drug Discovery, Institute for Scientific Research and High Technology Services (INDICASAT-AIP), City of Knowledge, Panama City, Republic of Panama.
- ^c Department of Biotechnology, Acharya Nagarjuna University, Nagarjuna Nagar, India.
- † Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/b000000x/
- (a) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.*, 2000, **100**, 3553–3590. (b) G. Chelucci and R. P. Thummel, *Chem. Rev.*, 2002, **102**, 3129. (c) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.*, 2010, **2**, 527–532.
- (a) L.-G. Ming, *Med. Res. Rev.*, 2003, **23**, 697–762. (b) I. Eryazici, C. N. Moorefield, G. R. Newkome, *Chem. Rev.*, 2008, **108**, 1834–1895.
- (a) O. M. Yaghi, H. Li, C. Davis, D. Richardson, T. L. Groy, *Acc. Chem. Res.*, 1998, **31**, 474–484. (b) H. Usta, A. Facchetti, T. J. Marks, *Acc. Chem. Res.*, 2011, **44**, 501–510.
- (a) K. Masui, H. Ikegami, A. Mori, *J. Am. Chem. Soc.*, 2004, **126**, 5074. (b) M. Takahashi, K. Masui, H. Sekiguchi, N. Kobayashi, A. Mori, M. Funahashi, N. Tamaoki, *J. Am. Chem. Soc.*, 2006, **128**, 10930–10933. (c) N.-N. Li, Y.-L. Zhang, S. Mao, Y.-R. Gao, D.-D. Guo, Y.-Q. Wang, *Org. Lett.*, 2014, **16**, 2732.
- R. Odani, M. Nishino, K. Hirano, T. Satoh, M. Miura, *Heterocycles*, 2014, **88**, 595–602.
- Z. Liang, J. Zhao, Y. Zhang, *J. Org. Chem.*, 2010, **75**, 170.
- Z. Liang, J. Zhao, Y. Zhang, *J. Org. Chem.*, 2010, **75**, 170.
- J.-B. Xia, X.-Q. Wang, S.-L. You, *J. Org. Chem.*, 2009, **74**, 456.
- (a) T. Truong, J. Alvarado, L. D. Tran, O. Daugulis, *Org. Lett.*, 2010, **12**, 1200. (b) D. Monguchi, A. Yamamura, T. Fujiwara, T. Somete, A. Mori, *Tetrahedron Lett.*, 2010, **51**, 850.
- (a) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Chem. Commun.*, 2012, 8105; (b) H. Yoshida, Y. Asatsu, Y. Mimura, Y. Ito, J. Ohshita, K. Takaki, *Angew. Chem., Int. Ed.*, 2011, **6**, 9676.
- D. E. Stephens, J. Lakey-Beitia, A. C. Atesin, T. A. Atesin, G. Chavez, H. D. Arman, O. V. Larionov, *ACS Catal.*, 2015, **5**, 167–175. For additional work on C8–H functionalization of quinolines, see: (a) J. Kwak, M. Kim, S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 3780. (b) T. Shibata, Y. Matsuo, *Adv. Synth. Catal.*, 2014, **7**, 1516. (c) S. Konishi, S. Kawamori, T. Iwai, M. Sawamura, *Chem. Asian. J.*, 2014, **9**, 434. (d) H. Hwang, J. Kim, J. Jeong, S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 10770. (e) X. Zhang, Z. Qi, X. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 10794–10798. (f) J. Jeong, P. Patel, H. Hwang, S. Chang, *Org. Lett.*, 2014, **16**, 4598.
- For preparation of quinoline *N*-oxides, see: (a) C. Coperet, H. Adolfsson, T.-A. W. Khuong, A. K. Yudin, K. B. Sharpless, *J. Org. Chem.*, 1998, **63**, 1740. (b) O. V. Larionov, D. Stephens, A. M. Mfuh, H. D. Arman, A. S. Naumova, G. Chavez, B. Skenderi, *Org. Biomol. Chem.*, 2014, **12**, 3026.

- 13 (a) P. R. Blakemore, C. Kilner, S. D. Milicevic, *J. Org. Chem.*, 2006, **71**, 8212. (b) S. S. Milicevic, C. Wang, L. N. Zakharov, P. R. Blakemore, *Eur. J. Org. Chem.*, 2012, 3249. (c) C. Wang, D. M. Flanigan, L. N. Zakharov, P. R. Blakemore, *Org. Lett.*, 2014, **13**, 4024. (d) Z. H. Wu, C. Wang, L. N. Zakharov, P. R. Blakemore, *Synthesis*, 2014, **46**, 678.
- 14 (a) A. Jossang, M. Boeuf, A. Cavé, *J. Nat. Prod.*, 1986, **49**, 1028. (b) S. Ruchirawat, S. Predapitakkun, *Heterocycles*, 2001, **55**, 371.
- 15 (a) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 14047. (b) F. Saito, H. Aiso, T. Kochi, F. Kakiuchi, *Organometallics*, 2014, **33**, 6704–6707.
- 16 R. Grainger, J. Cornella, D. C. Blakemore, I. Larrosa, J. M. Campanera, *Chem. Eur. J.*, 2014, **20**, 16680–16687.
- 17 J.-B. Rouchet, C. Schneider, C. Spitz, J. Lefèvre, G. Dupas, C. Fruit, C. Hoarau, *Chem. Eur. J.*, 2014, **20**, 3610.
- 18 K. Shichiri, K. Funakoshi, S. Saeki, M. Hamana, *Chem. Pharm. Bull.*, 1980, **28**, 493.
- 19 J. Yin, B. Xiang, M. A. Huffman, C. E. Raab, I. W. Davies, *J. Org. Chem.*, 2007, **72**, 4554.
- 20 K. Konno, K. Hashimoto, H. Shirahama, T. Matsumoto, *Heterocycles*, 1986, **24**, 2169.
- 21 O. V. Larionov, D. Stephens, A. Mfuh, G. Chavez, *Org. Lett.*, 2014, **16**, 864.
- 22 K. Konno, K. Hashimoto, H. Shirahama, T. Matsumoto, *Heterocycles*, 1986, **24**, 2169.
- 23 D. E. Stephens, G. Chavez, M. Valdes, M. Dovalina, H. Arman, O. V. Larionov, *Org. Biomol. Chem.*, 2014, **12**, 6190.
- 24 A. D. Ryabov, *Inorg. Chem.*, 1987, **26**, 1253.
- 25 S. Shekhar, J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 13016.
- 26 see Supporting Information.
- 27 For a discussion of the role of Ag^I as a single-electron oxidant in formation of Pd^{III} intermediates, see: D. C. Powers and T. Ritter. *Top. Organomet. Chem.*, **2011**, **35**, 129–156. For a similar observation of the role of AgF in the oxidative C–H-homocoupling of thiophenes, see ref. 4a.