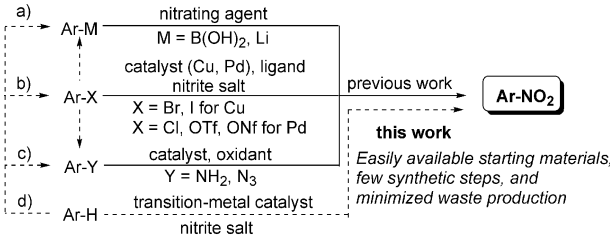
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002581

Regiospecific Synthesis of Nitroarenes by Palladium-Catalyzed Nitrogen-Donor-Directed Aromatic C–H Nitration

Yun-Kui Liu,* Shao-Jie Lou, Dan-Qian Xu, and Zhen-Yuan Xu*[a]

Aromatic nitro compounds are fundamental raw materials in the production of dyes, plastics, perfumes, explosives, and pharmaceuticals.[1] The nitrating agent-mediated electrophilic aromatic substitution has long been the classical synthetic approach for the preparation of nitroarenes.[2] However, there are several persistent problems, such as unsatisfactory regioselectivity, as well as imperfect functional group and/or substrate (especially for heteroaromatics) compatibility, that are always associated with the nitration processes. Besides, the site at which a nitro group is introduced largely depends on the orientation effect of different functional groups. To overcome these central challenges, several strategic approaches have recently been developed including an *ipso*-nitration protocol[3] by the nitrodemetalation of an aryl C–M bond (M = B, Li) (Scheme 1a)[4,5] or by transition-metal catalyzed (Cu or Pd) transformation of aryl halides, triflates, and nonaflates to nitroarenes developed by Saito[6] and Buchwald,[7] respectively (Scheme 1b), and an indirect nitration protocol involving the *ipso*-oxidation of an amino or azide group to a nitro group (Scheme 1c).[8,9] Although these strategies can completely or partially overcome the abovementioned problems and serve as promising approaches for the synthesis of nitroarenes, they all suffer from the use of prefunctionalized starting materials. In view of the encouraging achievements made in recently popularized C–H activation reactions,[10] we envisioned that transition metal-catalyzed direct cross-coupling between an Ar–H and a nitrite anion in a site-selective manner would be an ideal alternative approach to access nitroarenes (Scheme 1d).[11] Herein, we report on the first example of a palladium-catalyzed direct *ortho*-nitration of aryl C–H bonds in a series of azaarenes using a nitrogen donor as the directing functional group.[12,13]



Scheme 1. Strategies for the regioselective synthesis of nitroarenes.

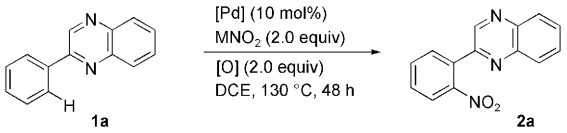
Our study commenced with the direct *ortho*-nitration of a quinoxaline-tethered aromatic ring mainly due to the potential uses of quinoxaline derivatives[14] in materials science, chemical, and pharmaceutical fields.[15] When model substrate **1a** was subjected to cross-coupling conditions with $NaNO_2$ in 1,2-dichloroethane (DCE) catalyzed by $Pd(OAc)_2$ (10 mol%) with $K_2S_2O_8$ (2.0 equiv) as an oxidant, the *ortho*-nitration product **2a** was indeed isolated in 28% yield (Table 1, entry 1). However, it seemed that the reaction was sensitive to several factors including the palladium and nitrite sources, oxidants, and solvents. Through systematically screening these parameters,[16] we were finally able to establish optimized reaction conditions under which **1a** cross-coupled with $AgNO_2$ to give the target product **2a** in 86% yield (Table 1, entry 4).

With optimized reaction conditions in hand, the scope of the Pd-catalyzed *ortho*-nitration of quinoxaline derivatives **1** with $AgNO_2$ was investigated (Table 2).[16] It was found that electron-rich aryl rings generally afforded the target products in moderate to high yields (76–93%; Table 2, entries 1–7). The present procedure also enabled the *ortho*-nitration of electron-deficient aryl rings, albeit with lower yields (35–51%; Table 2, entries 8–10, 12). A heterocyclic ring, namely thiophene, was *ortho*-nitrated in 35% yield (Table 2, entry 14). However, a furyl ring failed to be nitrated (Table 2, entry 15). Notably, a series of functional groups, in-

[a] Prof. Dr. Y.-K. Liu, Dr. S.-J. Lou, Prof. Dr. D.-Q. Xu, Z.-Y. Xu
State Key Laboratory Breeding Base
of Green Chemistry-Synthesis Technology
Zhejiang University of Technology
Hangzhou, 310014 (China)
Fax: (+86) 571-8832-0066
E-mail: ykuiliu@zjut.edu.cn
greensyn@zjut.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002581.

Table 1. Selected conditions for aryl C–H bond nitration.[a]



Entry	[Pd]	MNO_2/[O]	Yield [%][b]
1	$Pd(OAc)_2$	$NaNO_2/K_2S_2O_8$	28
2	$Pd(OAc)_2$	KNO_2[c]/$K_2S_2O_8$	trace
3	$Pd(OAc)_2$	$(TBA)NO_2/K_2S_2O_8$	trace
4	$Pd(OAc)_2$	$AgNO_2/K_2S_2O_8$	86(45[d])
5	$Pd(OAc)_2$	$AgNO_2$/Oxone	82
6	$Pd(OAc)_2$	$AgNO_2$/CAN	73
7	$Pd(OAc)_2$	$AgNO_2$/BQ	trace
8	$Pd(OAc)_2$	$AgNO_2/PhI(OAc)_2$	<5
9	$Pd(OAc)_2$	$AgNO_2/Cu(OAc)_2$	12
10	$PdCl_2$	$AgNO_2/K_2S_2O_8$	39
11	$Pd(OAc)_2$/2,2′-bipyridyl[e]	$AgNO_2/K_2S_2O_8$	<5
12	$[PdCl_2(PPh_3)_2]$	$AgNO_2/K_2S_2O_8$	56
13	–	$AgNO_2/K_2S_2O_8$	0

[a] Reaction conditions: compound **1a** (0.3 mmol), [Pd] (0.03 mmol), MNO_2 (0.6 mmol), [O] (0.6 mmol) in DCE (3.5 mL) at 130 °C for 48 h. [b] Yield of the isolated product. [c] [18]Crown-6 (0.6 mmol) was added as a phase-transfer catalyst (PTC). [d] $AgNO_2$ (0.3 mmol) and $K_2S_2O_8$ (0.3 mmol) were used. [e] 0.036 mmol of 2,2′-bipyridyl. TBA = tetrabutylammonium, CAN = ceric ammonium nitrate, BQ = *p*-benzoquinone.

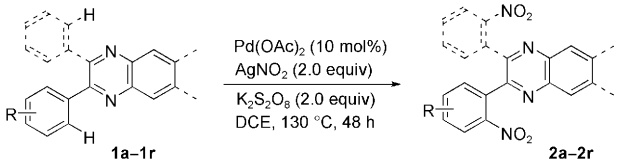
cluding methoxy (Table 2, entries 3–5), hydroxyl (entry 6), halo (F, Cl, Br, entries 8–10), and acetoxy (entry 12) were well tolerated under the reaction conditions, which would provide opportunities for further functionalization. Double-centered C–H nitration directed by each nitrogen donor in the quinoxaline moiety was also feasible (Table 2, entries 17 and 18).

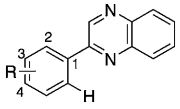
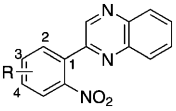
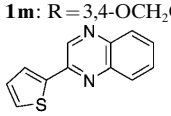
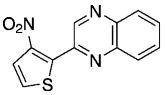
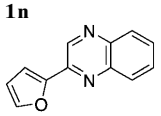
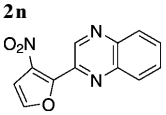
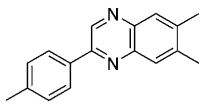
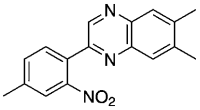
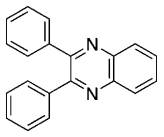
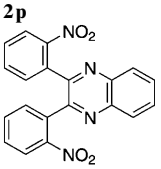
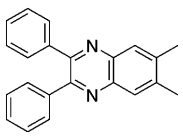
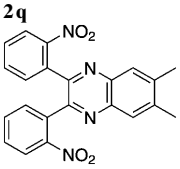
Next, exploration of the present nitrating protocol for other N-donor tethered aromatics (e.g., 2-arylpyridines, benzo[*h*]quinoline, and 2-arylpyrazoles) was carried out (Table 3), and the desired nitroarenes were obtained in 32–61% yields (Table 3, entries 1–9).[16] Among all surveyed donors at the present stage, quinoxaline represented the most effective directing group for the C–H nitration. In all cases, the reaction gave mononitration products predominantly (>95%). The *ortho*-regiochemistry of the nitrating reaction was unambiguously established on the basis of the spectral analyses, which was further confirmed by X-ray diffraction analysis of a related derivative **2c** (Figure 1).

To test whether the present strategy could be applied in the regioselective nitration of removable N-donor tethered aromatics, acetophenone *O*-methyl oximes were prepared. Gratifyingly, 2-nitrated acetophenones were conveniently prepared from the corresponding acetophenones in a three-step process (Scheme 2), which is difficult using traditional nitrating processes.

Finally, preliminary experiments were performed to gain a mechanistic insight into the C–H nitration.[16] A binuclear palladacycle **9** originating from **3a** also catalyzed the nitration reaction (**4a**: 67% yield as determined by GC).[17] The reaction exhibited a primary kinetic isotope effect both in the intramolecular ($k_H/k_D = 5.3$) and intermolecular ($k_H/k_D =$ 4.6) competition experiments, consistent with a rate-determining cyclopalladation step. When the reaction was performed under the standard conditions in the presence of

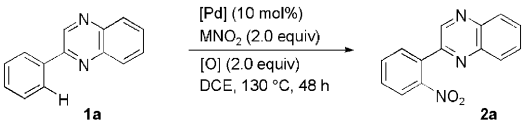
Table 2. Pd-catalyzed *ortho*-nitration of aromatic C–H bonds directed by a quinoxaline ligand.[a]

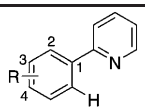
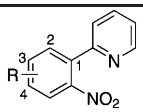
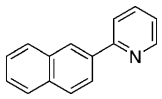
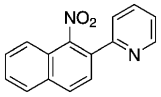
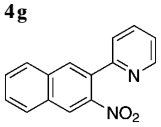
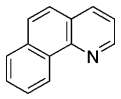
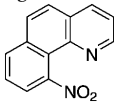
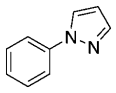
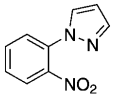


Entry	Substrate **1**	Product **2**	Yield [%][b]
			
	1a–1m	**2a–2m**	
1	**1a**: R = H	**2a**	86
2	**1b**: R = 4-Me	**2b**	76
3	**1c**: R = 4-OMe	**2c**	88
4	**1d**: R = 2-OMe	**2d**	93
5	**1e**: R = 3-OMe	**2e**	82
6	**1f**: R = 4-OH	**2f**	81[c]
7	**1g**: R = 4-Ph	**2g**	87
8	**1h**: R = 4-F	**2h**	35
9	**1i**: R = 4-Cl	**2i**	44
10	**1j**: R = 4-Br	**2j**	50
11	**1k**: R = 4-CN	**2k**	0
12	**1l**: R = 2-OAc	**2l**	51
13	**1m**: R = 3,4-OCH_2O	**2m**	0
14			35
	1n	**2n**	
15			0
	1o	**2o**	
16			46
	1p	**2p**	
17			60[d]
	1q	**2q**	
18			55[d]
	1r	**2r**	

[a] Reaction conditions: Compound **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol) in DCE (3.5 mL) at 130 °C for 48 h. [b] Yield of the isolated product. [c] $AgNO_2$ (0.3 mmol) and $K_2S_2O_8$ (0.3 mmol) were used. [d] $AgNO_2$ (0.9 mmol), $K_2S_2O_8$ (0.9 mmol), and $Pd(OAc)_2$ (0.045 mmol) were used.

Table 3. Pd-catalyzed *ortho*-nitration of the aromatic C–H bond in **3** directed by other nitrogen donors.[a]



Entry	Substrate **1**	Product **2**	Yield [%][b]
			
	3a–3f	**4a–4f**	
1	**3a**: R = H	**4a**	42
2	**3b**: R = 2-Me	**4b**	32
3	**3c**: R = 4-F	**4c**	56
4	**3d**: R = 4-Cl	**4d**	52
5	**3e**: R = 3-Cl	**4e**	38
6	**3f**: R = 4-Br	**4f**	57
7	 **3g**	 **4g**  **4g′**	45 (1:1)[c]
8	 **3h**	 **4h**	61[d]
9	 **3i**	 **4i**	55[d]

[a] Reaction conditions: Compound **3** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol) in DCE (3.5 mL) at 130 °C for 48 h. [b] Yield of the isolated product. [c] Determined on the basis of ^1H NMR spectroscopic analysis. [d] CAN (0.6 mmol) was used as the oxidant.

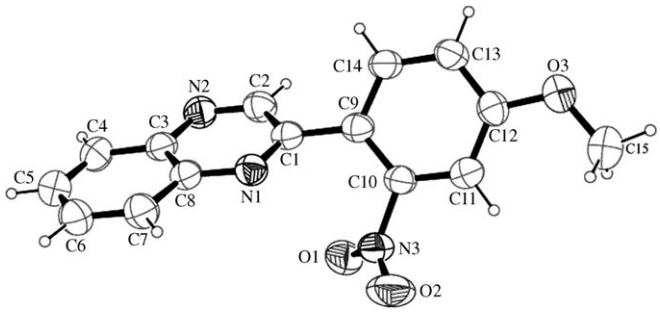
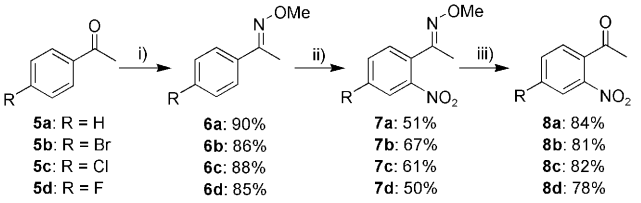
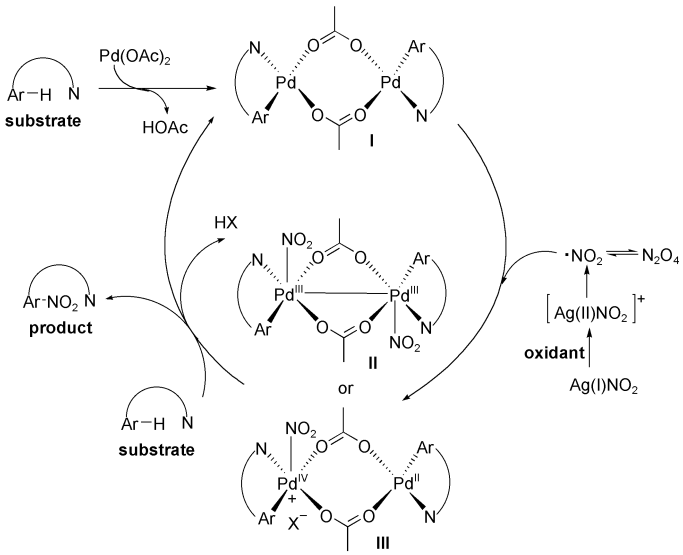


Figure 1. X-ray crystal structure of nitroarene **2c**. Ellipsoids at 50 % probability.

TEMPO (2.0 equiv), a radical scavenger,[18] the reaction failed to give any nitrated products, supporting a silver-mediated radical mechanism[11a,19,20] involving palladium(II/III)[13b–c] and/or palladium(II/IV)[13a,21] catalytic cycles under oxidizing conditions (Scheme 3).[13d–e]



Scheme 2. Synthesis of 2-nitrated acetophenones from acetophenones. Reaction conditions: i) Compound **5** (0.04 mol), $MeONH_2$·HCl (1.2 equiv), pyridine (15 mL), methanol (100 mL), reflux, overnight. ii) Compound **6** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol) in DCE (3.5 mL) at 130 °C for 48 h. iii) Compound **7** (1.0 mmol), 12 M HCl (4 mL), Et_2O (4 mL), RT for 24 h.



Scheme 3. Proposed mechanism.

In summary, we have described a highly regioselective approach to nitroarenes involving palladium-catalyzed direct *ortho*-nitration of aromatic C–H bonds guided by a nitrogen functional group. This new approach to nitroarenes has characteristic advantages: 1) the direct use of azaarenes as substrates, without the need for prefunctionalization; 2) high mononitration selectivity and regiospecific nitration in the *ortho*-position relative to the nitrogen donors, independent of the effect of other functionalities; 3) broad functional group tolerance and, in particular, compatibility with N-heteroaromatics under neutral conditions. Further studies will focus on the investigation of the mechanism, as well as the exploration of this approach for the development of new ligand-directed and/or new metal-catalyzed C–H nitrations.

Experimental Section

Typical procedure for the palladium-catalyzed C–H nitration: Compound **1a** (61.8 mg, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $AgNO_2$ (92.3 mg,

0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), and anhydrous DCE (3.5 mL) were sequentially added to a 10 mL tube. Then the tube was sealed and stirred at 130 °C for 48 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100–200 mesh) with petroleum ether/EtOAc (4:1, v/v) as eluent to give the desired product **2a** 64.8 mg (86%) as a pale yellow solid.

CCDC-781968 contains the supplementary crystallographic data for **2c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We gratefully thank the Natural Science Foundation of Zhejiang Province (grant no.: Y4100201), the Foundation of Education of Zhejiang Province (grant no.: Z200803599), Science and Technology Department of Zhejiang Province and the Opening Foundation of Zhejiang Provincial Top Key Discipline for financial support.

Keywords: C–H activation · heterocycles · nitroarenes · palladium · regioselectivity

[1] a) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**; b) H. Feuer, A. T. Nielson, *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, Weinheim, **1990**.

[2] a) G. A. Olah, R. Malhotra, S. C. Narang, *Nitration: Methods and Mechanisms*, VCH, Weinheim, **1989**; b) K. Schofield, *Aromatic Nitration*, Cambridge University Press, Cambridge, **1980**.

[3] For a recent highlight article on *ipso*-nitration, see: G. K. S. Prakash, T. Mathew, *Angew. Chem.* **2010**, *122*, 1771; *Angew. Chem. Int. Ed.* **2010**, *49*, 1726.

[4] a) S. Stefan, S. Jurgen, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *Synlett* **2000**, 1485; b) G. K. S. Prakash, C. Panja, T. Mathew, V. Surampud, N. A. Petasis, G. A. Olah, *Org. Lett.* **2004**, *6*, 2205.

[5] K. Tani, K. Lukin, P. E. Eaton, *J. Am. Chem. Soc.* **1997**, *119*, 1476.

[6] S. Saito, Y. Koizumi, *Tetrahedron Lett.* **2005**, *46*, 4715.

[7] B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 12898.

[8] K. R. Reddy, C. U. Maheswari, M. Venkateshwar, L. Kantam, *Adv. Synth. Catal.* **2009**, *351*, 93, and references therein.

[9] S. Rozen, M. Carmeli, *J. Am. Chem. Soc.* **2003**, *125*, 8118.

[10] For selected reviews on C–H activations, see: a) G. Dyker, *Handbook of C–H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim, **2005**; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; e) O. Daugulis, H.-Q. Do, D. Shabashow, *Acc. Chem. Res.* **2009**, *42*, 1074; f) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949; g) K. Godula, D. Sames, *Science* **2006**, *312*, 67; h) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041.

[11] For examples of stoichiometric amounts of redox metal complexes in the direct cross-coupling of Ar–H and nitrite anions, see: a) B. Birkmann, B. T. Owens, S. Bandyopadhyay, G. Wu, P. C. Ford, *J. Inorg. Biochem.* **2009**, *103*, 237; b) M. Stefanelli, M. Mastroianni, S. Nardis, S. Licoccia, F. R. Fronczek, K. M. Smith, W. Zhu, Z. Ou, K. M. Kadish, R. Paolesse, *Inorg. Chem.* **2007**, *46*, 10791.

[12] For reviews on C–H aminations, see: a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; b) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439; c) H. M. L. Davies, M. S. Long, *Angew. Chem.* **2005**, *117*, 3584; *Angew. Chem. Int. Ed.* **2005**, *44*, 3518.

[13] For selected examples of nitrogen-donor-directed C–H functionalization, see: a) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234; b) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 17050; c) D. C. Powers, T. Ritter, *Nat. Chem.* **2009**, *1*, 302; d) W.-Y. Yu, W. N. Sit, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 3174; e) W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* **2008**, *130*, 3304; f) K. Cheng, B. Yao, J. Zhao, Y. Zhang, *Org. Lett.* **2008**, *10*, 5309.

[14] For examples of quinoxaline as an N donor for C–H activations, see: D. Schneidenbach, S. Ammermann, M. Debeaux, A. Freund, M. Zöllner, C. Daniliuc, P. G. Jones, W. Kowalsky, H.-H. Johannes, *Inorg. Chem.* **2010**, *49*, 397; also see reference [13f].

[15] a) K. R. J. Thomas, M. Velusamy, J. T. Lin, C.-H. Chuen, Y.-T. Tao, *Chem. Mater.* **2005**, *17*, 1860; b) A. Katoh, T. Yoshida, J. Ohkanda, *Heterocycles* **2000**, *52*, 911; c) L. E. Seitz, W. J. Suling, R. C. Reynolds, *J. Med. Chem.* **2002**, *45*, 5604.

[16] See the Supporting Information for details.

[17] Surprisingly, the stoichiometric reaction of **9** with $AgNO_2$ in the presence of $K_2S_2O_8$ gave no **4a**, see the Supporting Information for details. In a similar case none of the acetoxylated product was found in the stoichiometric reaction of **5** with $PhI(OAc)_2$, see reference [13b].

[18] For examples of the utilization of TEMPO as a radical scavenger, see: a) P. A. Sibbald, F. E. Michael, *Org. Lett.* **2009**, *11*, 1147; b) A. C. Albéniz, P. Espinet, R. López-Fernández, A. Sen, *J. Am. Chem. Soc.* **2002**, *124*, 11278.

[19] For silver-mediated radical reactions, see: a) F. Minisci, A. Citterio, *Acc. Chem. Res.* **1983**, *16*, 27; b) A. Kumar, P. Neta, *J. Am. Chem. Soc.* **1980**, *102*, 7284.

[20] For a review on the addition of ligand-centered radicals to organometallic complexes, see: K. E. Torraca, L. McElwee-White, *Coord. Chem. Rev.* **2000**, *206–207*, 469.

[21] For reviews on palladium(II/IV) catalytic cycles, see: a) L.-M. Xu, B.-J. Li, Z. Yang, Z.-J. Shi, *Chem. Soc. Rev.* **2010**, *39*, 712; b) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824; c) K. Muñiz, *Angew. Chem.* **2009**, *121*, 9576; *Angew. Chem. Int. Ed.* **2009**, *48*, 9412; d) N. R. Deprez, M. S. Sanford, *Inorg. Chem.* **2007**, *46*, 1924.

Received: September 6, 2010
Published online: November 9, 2010

