DOI: 10.1002/adsc.201200997

Palladium-Catalyzed Direct Denitrogenative C-3-Arylation of 1*H*-Indoles with Arylhydrazines using Air as the Oxidant

Yongxin Chen,[a] Shuaibo Guo,[a] Kangning Li,[a] Jinpeng Qu,[a] Hua Yuan,[a] Qiuru Hua,[a] and Baohua Chen[a,*]

[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Gansu Lanzhou, 730000, People's Republic of China and Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Lanzhou 730000, People's Republic of China
Fax: +(86)-931-891-2582; e-mail: chbh@lzu.edu.cn

Received: November 13, 2012; Revised: December 24, 2012; Published online: February 25, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200997.

Abstract: A novel palladium-catalyzed approach to direct C-3-arylation of 1*H*-indoles with arylhydrazines using air as the oxidant *via* C–N bond cleavage has been developed. Various substituents are tolerated in this system in moderate to good yields. This reaction could also be compatible with a larger scale. Thus, this strategy using arylhydrazines as arylating reagents provides a powerful method for constructing substituted 3-aryl-1*H*-indoles.

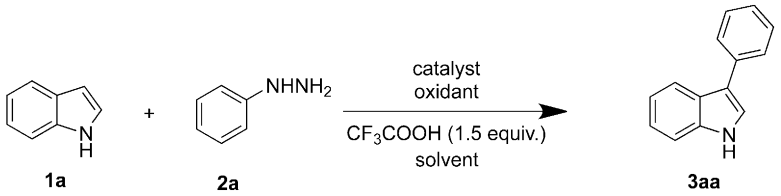
Keywords: arylhydrazines; 3-aryl-1*H*-indoles; C–H activation; denitrogenative process; palladium-catalyzed reaction

Transition metal-catalyzed C–C bond-forming reactions represent important and useful synthetic methods in organic synthesis,[1] which have widespread applications in medicinal chemistry and materials science.[2] Among them, using arylating reagents such as aryl halides, ArC(O)OH, and $ArSO_2X$ (X = H, Na, and $NHNH_2$) for direct arylation is one of the most powerful methods in the construction of C–C bonds.[3] Arylhydrazines as active compounds are used for preparing nitrogen-containing compounds[4] and generate radical species *via* oxidation.[5] Even so, little attention has been paid to utilize them as arylating reagents *via* denitrogenation. Recently, Loh and coworkers first reported the palladium-catalyzed C–C bond formation of arylhydrazines with olefins *via* C–N bond cleavage.[6]

Arylindole skeletons are ubiquitous in many biologically active natural products and pharmaceuticals.[7] They also exhibit a wide range of biological properties, such as antiprotozoal agents, h5-HT2A receptor antagonist, etc.[8] Therefore, considerable efforts have been focused on the direct and site-selective arylation of indoles with various arylating reagents.[9] Su and Larrosa independently synthesized arylindoles with benzoic acids as arylating reagents,[10] but the *ortho*-substituted benzoic acids were required for the transformations. Deng and co-workers developed a palladium-catalyzed cascade for the direct desulfitative C-2-arylation of indoles with sodium sulfinates.[11] However, most of them required N-protecting groups, high loading of metal oxidants, or harsh reaction conditions. Notably, apart from aryl halides,[12] only a few approaches to the direct C-3-arylation of 1*H*-indoles with arylating reagents have been reported.[13] Considering economical and environmental viewpoints, air serves as the ideal oxidant because of its abundance, lack of toxic by-products and is more applicable to industry.[14] Herein, as part of our ongoing study on the functionalization of heterocycles,[15] we report a facile and efficient method to synthesize 3-aryl-1*H*-indoles with arylhydrazines by using air as the oxidant.

To begin this study, 1*H*-indole (**1a**) and phenylhydrazine (**2a**) were chosen as model substrates to optimize the reaction conditions (Table 1). The desired product **3aa** was obtained in 78% yield in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% of 1,10-phenanthroline, and 1.5 equivalents of CF_3COOH in PhCl at 100 °C (Table 1, entry1). To improve the reaction efficiency, various oxidants were then investigated, but only inferior results were obtained (Table 1, entries 2–5). When O_2 was employed as the oxidant, 76% of **3aa** was isolated (Table 1, entry 6). To our delight, increasing the amount of 1,10-phenanthroline to 30 mol%, the yield of **3aa** resulted in 89%, while 2,2-bipy showed no better effect on the promotion of this reaction (Table 1, entries 7 and 8). Other palladium species such as $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(dba)_2$ were substantially less effective (Table 1, entries 9–11). Reducing the amount of $Pd(OAc)_2$ to 5 mol% led

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Ligand	Oxidant	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	1,10-Phen (20%)	air	PhCl	78
2	$Pd(OAc)_2$	1,10-Phen (20%)	$Cu(OAc)_2$	PhCl	0
3	$Pd(OAc)_2$	1,10-Phen (20%)	AgOAc	PhCl	15
4	$Pd(OAc)_2$	1,10-Phen (20%)	BQ	PhCl	trace
5	$Pd(OAc)_2$	1,10-Phen (20%)	$K_2S_2O_8$	PhCl	62
6	$Pd(OAc)_2$	1,10-Phen (20%)	O_2	PhCl	76
7	**$Pd(OAc)_2$**	**1,10-Phen (30%)**	**air**	**PhCl**	**89**
8	$Pd(OAc)_2$	2,2′-bipy (30%)	air	PhCl	18
9	$PdCl_2$	1,10-Phen (30%)	air	PhCl	37
10	$PdCl_2(PPh_3)_2$	1,10-Phen (30%)	air	PhCl	20
11	$Pd(dba)_2$	1,10-Phen (30%)	air	PhCl	65
12	$Pd(OAc)_2$	1,10-Phen (30%)	air	PhCl	67[c]
13	$Pd(OAc)_2$	1,10-Phen (30%)	air	PhMe	68
14	$Pd(OAc)_2$	1,10-Phen (30%)	air	DMF	0
15	$Pd(OAc)_2$	1,10-Phen (30%)	air	DCE	trace
16	$Pd(OAc)_2$	1,10-Phen (30%)	air	1,2-dichlorobenzene	60
17	$Pd(OAc)_2$	1,10-Phen (30%)	air	PhCl	30[d]/79[e]

[a] *Conditions:* **1a** (0.20 mmol), **2a** (0.40 mmol), catalyst (10 mol%), oxidant (2 equiv.), CF_3COOH (1.5 equiv.), solvent (1 mL), 12 h, 100 °C.
[b] Isolated yields after column chromatography.
[c] With 5 mol% $Pd(OAc)_2$.
[d] At 80 °C.
[e] At 120 °C.

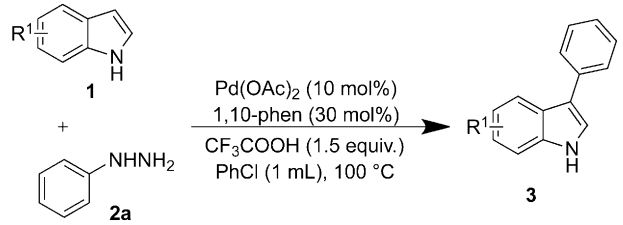
to a lower yield (Table 1, entry 12). Different solvents were also evaluated, and they showed disappointing results (Table 1, entries 13–16). The yield was found to decrease with the temperature changed to 80 or 120 °C (Table 1, entry 17). Additionally, the reaction was inefficient in the absence of $Pd(OAc)_2$ or CF_3COOH.

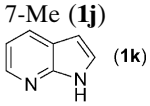
Under the optimized reaction conditions, a wide range of 1*H*-indoles were examined to establish the scope of this reaction (Table 2). Generally, various 1*H*-indoles with substituted groups such as methyl, methoxy, chloro, and 7-azaindole were compatible with the reaction conditions, affording the desired products in moderate to good yields. With indoles substituted at the 5-position, the electron-rich substituents showed better reactivities and gave higher yields than electron-deficient ones (Table 2, entries 2–6). Strongly electron-deficient nitro or cyano groups lowered the yield significantly even after a prolonged reaction time (Table 2, entries 7 and 8). Indoles with a methyl on the 6- or 7-position were also examined, and high yields were obtained (Table 2, entries 9 and 10). In addition, a heterocyclic indole, such as 7-azaindole (**1k**), could also be used in the reaction, resulting in the corresponding product **3ka** in 65% yield (Table 2, entry 11). Unfortunately, no desired products were observed when N-protected indoles were subjected to the optimized conditions.

The reaction scope was further expanded to substituted arylhydrazines **2** (Table 3). It was found that most arylhydrazines bearing *ortho*-, *meta*-, and *para*-substitutions provided moderate to good yields, and showed good functional group tolerance. Higher yields were obtained with electron-withdrawing substituents, and the yields were reduced significantly with methoxy groups (Table 3, entry 10). More importantly, halogen substituents in the substrate can also be well tolerated, allowing further coupling reactions for the synthesis of more complex molecules (Table 3, entries 1–3, 5, 11–14). More bulky substrates such as 1-naphthylhydrazine (**2m**) also could be transformed smoothly and afforded 3-(naphthalen-1-yl)-1*H*-indole in 63% yield (Table 3, entry 16).

This coupling reaction was also compatible with a larger scale under the optimized condition (Scheme 1). A mixture of 1*H*-indole (1 mmol), phenylhydrazine (2 mmol), $Pd(OAc)_2$ (10%, 22.5 mg), 1,10-phen (30%, 59.5 mg), CF_3COOH (1.5 equiv.,

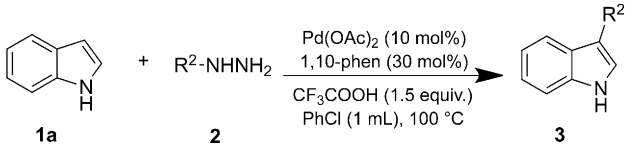
Table 2. Reactions of various 1*H*-indoles (**1**) with phenylhydrazine (**2a**).[a]



Entry	R^1	Product	Yield [%][b]
1	H (**1a**)	**3aa**	89
2	5-Me (**1b**)	**3ba**	91
3	5-OMe (**1c**)	**3ca**	82
4	5-F (**1d**)	**3da**	81
5	5-Cl (**1e**)	**3ea**	70
6	5-Br (**1f**)	**3fa**	78
7	5-CN (**1g**)	**3ga**	trace
8	5-NO_2 (**1h**)	**3ha**	trace[a]/18[c]
9	6-Me (**1i**)	**3ia**	79
10	7-Me (**1j**)	**3ja**	84
11	 (**1k**)	**3ka**	65[c]

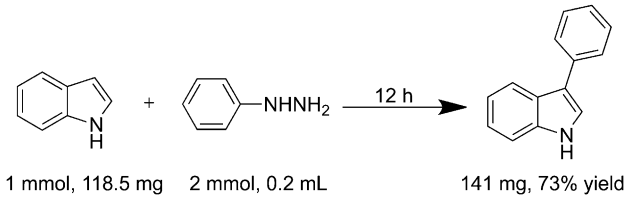
[a] *Conditions:* **1** (0.20 mmol), **2a** (0.40 mmol), $Pd(OAc)_2$ (10 mol%), 1,10-phen (30 mol%), CF_3COOH (1.5 equiv.), PhCl (1 mL), 12 h, 100 °C.
[b] Isolated yields after column chromatography.
[c] 24 h.

Table 3. Reactions of 1*H*-indole (**1a**) with various arylhydrazines (**2**).[a]



Entry	R^2	Product	Yield [%][b]
1	4-FC_6H_4 (**2b**)	**3ab**	81[c]
2	4-ClC_6H_4 (**2c**)	**3ac**	92[c]
3	4-BrC_6H_4 (**2d**)	**3ad**	95[c]
4	4-$CF_3C_6H_4$ (**2e**)	**3ae**	90[c]
5	3-Cl-4-$CH_3C_6H_3$ (**2f**)	**3af**	78[c]
6	4-$NO_2C_6H_4$ (**2g**)	**3ag**	0
7	4-$CH_3C_6H_4$ (**2h**)	**3ah**	74
8	4-*t*-BuC_6H_4 (**2i**)	**3ai**	74
9	2-$CH_3C_6H_4$ (**2j**)	**3aj**	85
10	2-$CH_3OC_6H_4$ (**2k**)	**3ak**	23
11	2-CH_3-5-Cl-C_6H_3 (**2l**)	**3al**	72[c]
12	2-ClC_6H_4 (**2m**)	**3am**	76[c]
13	3-ClC_6H_4 (**2n**)	**3an**	83[c]
14	3-BrC_6H_4 (**2o**)	**3ao**	89[c]
15	3-$CH_3C_6H_4$ (**2p**)	**3ap**	73
16	1-naphthyl (**2q**)	**3aq**	63

[a] *Conditions:* **1a** (0.20 mmol), **2** (0.40 mmol), $Pd(OAc)_2$ (10 mol%), 1,10-phen (30 mol%), CF_3COOH (1.5 equiv.), PhCl (1 mL), 12 h, 100 °C.
[b] Isolated yields after column chromatography.
[c] 17 h.



Scheme 1. Coupling of 1*H*-indole with phenylhydrazine on a larger scale.

112.5 μL), and PhCl (5 mL) was stirred at 100 °C for 12 h and afforded the desired product in 73% yield.

Based on the above results and research from other groups,[3i,6,10,11] a tentative reaction mechanism is illustrated in Scheme 2. Initially, the metathesis of substrate **2a** and $Pd(II)_2L_2$ affords palladiaziridine complex **A** that has been established by Muñiz,[16] and then oxidative addition of complex **A** with $Pd(0)L_2$ forms the two palladium(II) centered complex **B** *via* C–N bond cleavage, which was proposed by Loh.[6] Subsequent protonolysis of **B** gives the aryl palladium complex **C** and the palladiaziridine complex **D**. Next, **C** is attacked by 1*H*-indole **1a** *via* C–H activation to generate a palladium(II) aryl heteroaryl intermediate (**E**), which would undergo C–C reductive elimination to produce the target product **3aa** and $Pd(0)L_2$. **D** is decomposed into $Pd(0)L_2$, N_2, and H_2O by air. Finally, the Pd(0) species is reoxidized to Pd(II) by air with the assistance of a ligand.

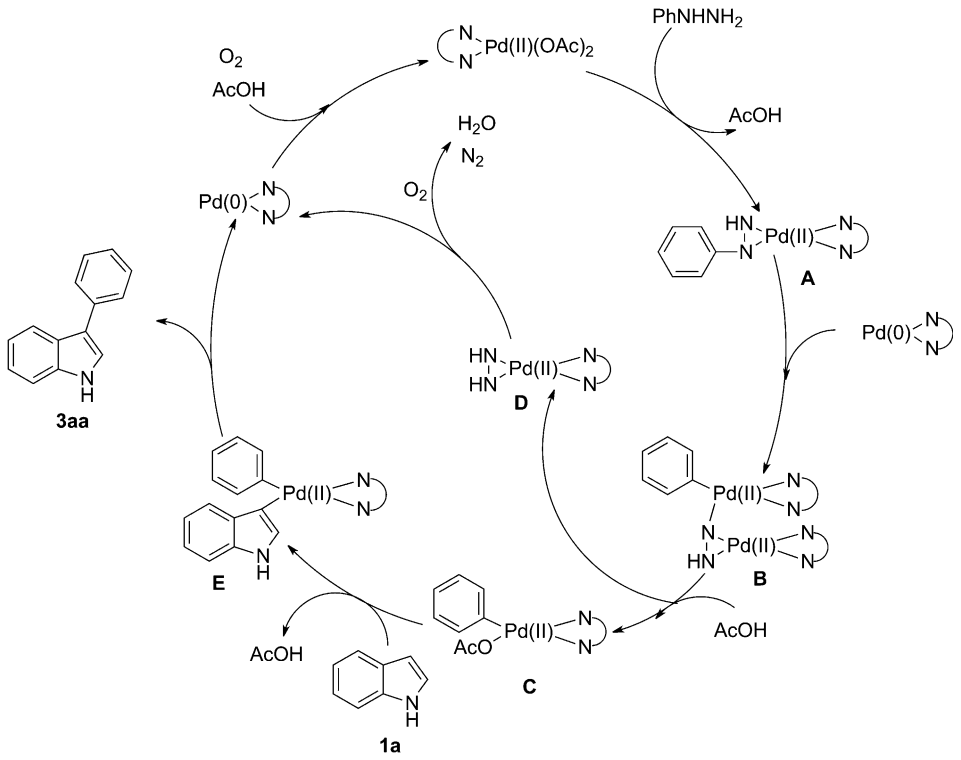
In summary, we have demonstrated a novel Pd-catalyzed direct denitrogenative C-3-arylation of indoles with arylhydrazines. The procedure, using air as the oxidant, is a simple, economical, and environmentally friendly protocol, which could be applied to various available substrates in moderate to good yields. This approach is a useful strategy to develop new arylating reagents for the preparation of 3-aryl-1*H*-indoles.

Experimental Section

CAUTION: Arylhydrazines should be handled with care due to possible toxicity and carcinogenicity.

Typical Procedure for the Preparation of 3-Aryl-1*H*-indoles 3

1*H*-Indole **1** (0.20 mmol), arylhydrazine **2** (0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mmol%), 1,10-phen (11.9 mg, 30 mmol%), CF_3COOH (22.5 μL, 1.5 equiv.), and PhCl (1 mL) were added to a flask with a magnetic stirring bar. The resulting mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was diluted with



Scheme 2. A tentative reaction mechanism.

ethyl acetate and filtered. The filtrate was evaporated under reduced pressure to get the crude product, which was further purified by silica gel chromatography to give product **3**.

Acknowledgements

We are grateful for support of this project by National Science Foundation of P. R. China (No. J1103307).

References

[1] a) S. R. Dubbaka, P. Vogel, *Angew. Chem.* **2005**, *117*, 7848; *Angew. Chem. Int. Ed.* **2005**, *44*, 7674; b) J. Q. Yu, Z. J. Shi, *C–H Activation*, Springer, Berlin, **2010**; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; d) *Transition Metals for Organic Synthesis*, (Eds.: M. Beller, C. Bolm), 2nd edn., Wiley-VCH, Weinheim, **2004**; e) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.

[2] a) P. Bordat, R. Brown, *Chem. Phys. Lett.* **2000**, *331*, 439; b) A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101; c) A. C. Hiller, G. A. Grassa, M. S. Viciu, H. M. Lee, C. Yang, S. P. Nolan, *J. Organomet. Chem.* **2002**, *653*, 69.

[3] a) F. Le Callonnec, E. Fouquet, F.-X. Felpin, *Org. Lett.* **2011**, *13*, 2646; b) L. J. Gooßen, J. Paetzold, *Angew. Chem.* **2004**, *116*, 1115; *Angew. Chem. Int. Ed.* **2004**, *43*, 1095; c) A. Inoue, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **2003**, *125*, 1484; d) C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2011**, *17*, 761; e) S. Ranjit, X. Liu, *Chem. Eur. J.* **2011**, *17*, 1105; f) G.-W. Wang, T. Miao, *Chem. Eur. J.* **2011**, *17*, 5787; g) F.-L. Yang, X.-T. Ma, S.-K. Tian, *Chem. Eur. J.* **2012**, *18*, 1582; h) R. Chen, S. Liu, X. Liu, L. Yang, G.-J. Deng, *Org. Biomol. Chem.* **2011**, *9*, 7675; i) X. Yu, X. Li, B. Wan, *Org. Biomol. Chem.* **2012**, *10*, 7479; j) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

[4] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241; b) M. Zora, A. Kivrak, *J. Org. Chem.* **2011**, *76*, 9379.

[5] a) A. S. Demir, E. Özgül-Karaaslan *J. Chem. Soc. Perkin Trans. 1* **2001**, 3042; b) A. S. Demir, Ö. Reis, M. Emrullahoğlu, *Tetrahedron* **2002**, *58*, 8055; c) Z.-X. Chen, G.-W. Wang, *J. Org. Chem.* **2005**, *70*, 2380; d) H. Jasch, J. Scheumann, M. R. Heinrich, *J. Org. Chem.* **2012**, *77*, 10699.

[6] M.-K. Zhu, J.-F. Zhao, T.-P. Loh, *Org. Lett.* **2011**, *13*, 6308.

[7] a) A. Brancale, R. Silvestri, *Med. Res. Rev.* **2007**, *27*, 209; b) Y.-X. Zhang, Y. Chen, X.-N. Guo, X.-W. Zhang, W.-M. Zhao, L. Zhong, J. Zhou, Y. Xi, L.-P. Lin, J. Ding, *Anti-Cancer Drugs* **2005**, *16*, 515.

[8] a) S. L. Colletti, C. Li, M. H. Fisher, M. J. Wyvratt, P. T. Meinke, *Tetrahedron Lett.* **2000**, *41*, 7825; b) G. I. Stevenson, A. L. Smith, S. Lewis, S. G. Michie, J. G. Neduvelil, S. Patel, R. Marwood, S. Patel, J. L. Castro, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2697.

[9] a) M. A. Pena, J. P. Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2007**, *72*, 1271; b) F. Shibahara, E. Yamaguchi, T. Murai, *Chem. Commun.* **2010**, 2471; c) Z. Zhang, Z. Hu, Z. Yu, P. Lei, H. Chi, Y. Wang, R. He, *Tetrahedron Lett.* **2007**, *48*, 2415; d) Z. Liang, J. Zhao, Y. Zhang, *J. Org. Chem.* **2010**, *75*, 170; e) S. D. Yang, C. L. Sun, Z.

Fang, B. J. Li, Y. Li, Z. J. Shi, *Angew. Chem.* **2008**, *120*, 1495; *Angew. Chem. Int. Ed.* **2008**, *47*, 1473.
[10] a) J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang, W. Su, *Chem. Eur. J.* **2010**, *16*, 5876; b) J. Cornella, P. Lu, L. Larrosa, *Org. Lett.* **2009**, *11*, 5506.
[11] M. Wu, J. Luo, F. Xiao, S. Zhang, G.-J. Deng, H.-A. Luo, *Adv. Synth. Catal.* **2012**, *354*, 335.
[12] a) G. Cusati, L. Djakovitch, *Tetrahedron Lett.* **2008**, *49*, 2499; b) F. Bellina, F. Benelli, R. Rossi, *J. Org. Chem.* **2008**, *73*, 5529; c) A. Lutz, B. Sebastian, *Synlett* **2009**, 808; d) L. Joucla, N. Batail, L. Djakovitch, *Adv. Synth. Catal.* **2010**, *352*, 2929.
[13] a) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172; b) L. Ackermann, M. Dell'Acqua, S. Fenner, R. Vicente, R. Sandmann, *Org. Lett.* **2011**, *13*, 2358; c) D. H. R. Bartona, J.-P. Fineta, J. Khamsia, *Tetrahedron Lett.* **1988**, *29*, 1115; d) D. H. R. Bartona, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, W. B. Motherwell, M. T. B. Papoula, S. P. Stanforth, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2667.
[14] a) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem.* **2011**, *123*, 11256; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; b) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400.
[15] a) W. Chen, R. Yan, D. Tang, S. Guo, X. Meng, B. Chen, *Tetrahedron* **2012**, *68*, 7956; b) X. Meng, X. Li, W. Chen, Y. Zhang, W. Wang, J. Chen, J. Song, H. Feng, B. Chen, *J. Heterocycl. Chem.* DOI 10.1002/jhet.1616; c) X. Liu, Y. Chen, K. Li, D. Wang, B. Chen, *Chin. J. Chem.* **2012**, *30*, 2285.
[16] K. Muñiz, M. Nieger *Angew. Chem.* **2006**, *118*, 2363; *Angew. Chem. Int. Ed.* **2006**, *45*, 2305.

