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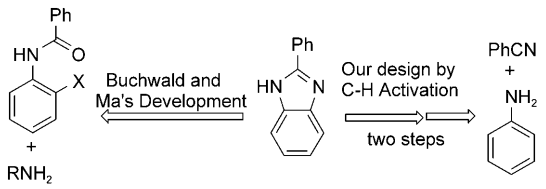
Direct Imidation to Construct 1*H*-Benzo[*d*]imidazole through Pd^{II}-Catalyzed C–H Activation Promoted by Thiourea

Qing Xiao, Wen-Hua Wang, Gang Liu, Fan-Ke Meng, Jia-Hua Chen, Zhen Yang,* and Zhang-Jie Shi*[a]

A novel and straightforward method to construct 1*H*-benzo[*d*]imidazole was developed b means of Pd^{II}-catalyzed intramolecular C–H activation starting from readily available *N*-phenylbenzimidamide. The detailed mechanism studies indicated that a palladacycle monomer or dimer is the key intermediate for this transformation and thiourea was first used to prompt the efficiency of C–H activation.

Much attention has been paid to C–N formation in the past two decades. Many useful methods have been developed to construct C–N bonds through transition-metal-catalyzed amination/amidation from aryl halides.[1] Very recently, new methods have been developed to construct C–N bonds intra/intermolecularly through direct aromatic C–H functionalization. Among these investigations, Buchwald and co-workers pioneered studies to construct a carbazole core structure through Pd^{II}-catalyzed intramolecular C–H activation.[2] Shortly afterwards, Che, Yu, and co-workers reported the intermolecular C–N formation through Pd^{II}- or Cu^{II}-catalyzed C–H functionalization, respectively.[3] When we were preparing this manuscript, Buchwald and co-workers reported a novel Cu-catalyzed direct C–H functionalization to produce benzimidazoles similar to our design. In their report, steric hindered benzimidamides showed the excellent reactivities to facilitate this transformation.[4] Herein we report a new method to construct 1*H*-benzo[*d*]imidazole through Pd^{II}-catalyzed intramolecular C–N formation, in which not only the substrate scope was widely extended, but also thiourea (tetramethylthiourea, TMTU) was introduced for the first time as an additive to promote the efficiency of the Pd^{II} catalysis for the direct C–H transformation.

1*H*-benzo[*d*]imidazole (**1a**) is a unique structural unit of many natural products and synthetic drugs.[5] This scaffold can be obtained starting from benzene-1,2-diamine and its derivatives.[6] Very recently, Ma and Buchwald made significant contributions to constructing this useful scaffold through Pd- or Cu-catalyzed tandem reactions starting from amines and *ortho*-haloacetanilides,[7] which are readily available through the developed highly selective halogenation of acetanilides.[8] Undoubtedly, the most straightforward method to construct this scaffold is to construct C–N bond directly through highly selective C–H activation from the aniline derivatives (Scheme 1).



Scheme 1. New strategies to construct benzoimidazole through C–H activation.

N-Arylbenzimidamide **2** was readily synthesized through the addition of aniline to benzonitrile according to the referenced method.[9] To verify our supposition, we first conducted the stoichiometric reaction starting from **2a** in the presence of one equivalent of $PdCl_2$. Gratifyingly, the palladacycle dimer **3** was obtained, the structure of which was further determined by X-ray crystallography. This dimer could further undergo reductive elimination to form the designed product **1a** in DMSO in low yield in the presence of NaOAc with the recovery of the starting material **2a** in the absence of any oxidants (Scheme 2). Although the efficiency

[a] Q. Xiao, W.-H. Wang, G. Liu, F.-K. Meng, Prof. Dr. J.-H. Chen, Dr. Z. Yang, Prof. Dr. Z.-J. Shi
Key Laboratory of Bioorganic Chemistry and Molecular Engineering of the Ministry of Education
College of Chemistry and Green Chemistry Center
Peking University, Beijing 100871,
Fax: (+86) 106-276-0890
E-mail: zshi@pku.edu.cn
zyang@pku.edu.cn

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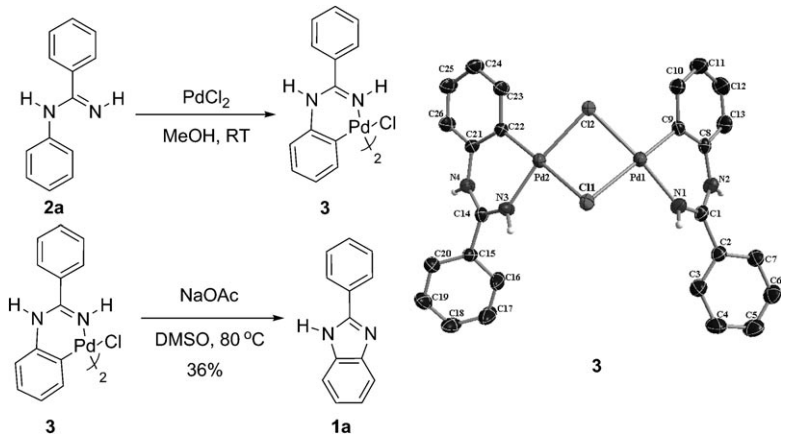


Scheme 2. First try towards **1a** with stoichiometric palladacycle dimer **3**.

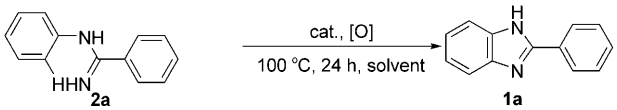
of this transformation was quite low, we assumed that it is theoretically reasonable to synthesize 1*H*-benzo[*d*]imidazoles (**1**) starting from *N*-phenylbenzimidamides (**2**) through Pd^{II}-catalyzed, direct C–H transformation directed by the imino group with proper oxidants on the basis of these studies.

We started looking for the catalytic version for this transformation. After systematic investigation, imidazole **1a** was obtained in the presence of $[PdCl_2(PhCN)_2]$ as the catalyst and $Cu(OAc)_2/O_2$ as a co-oxidant in NMP (Table 1; NMP = *N*-methyl-2-pyrrolidone). During this transformation, TMTU was used for the first time to promote the efficiency in C–H transformation as an additive, although thiourea has been broadly used as a ligand in different transformations.[10] The yield decreased dramatically in the absence of TMTU, which may arise from the stabilizing ability of TMTU to Pd^{II} species (cf. entries 5 and 13). Interestingly, $Cu(OAc)_2$ itself could promote this transformation, but the efficiency was very low under our developed conditions (entry 1). It is of great importance to note that DMSO is also a suitable solvent and the desired product could be obtained in a good yield. However, the impurity (dimethylsulfone) from DMSO could not be separated after many trials (entry 20). Other palladium species lowered the catalytic efficiency more or less. Furthermore, different organic and inorganic oxidants were tested, but failed for this transformation. In addition, the catalyst loading could be decreased to 5 mol% with a slightly lower yield.

The influence of substitutions on the nitrile moiety was first investigated (Table 2). Only electron-donating groups on phenyl ring were compatible with this transformation (entries 2–7). When a strong electron-donating group was introduced to benzonitrile fragment, the efficiency was enhanced even at low temperature (entries 4–6). The steric effect did not affect the efficiency of this transformation. In addition, *ortho*-substituents promoted the yield (entry 2). It is worth noting that C–Cl was compatible with our reaction conditions and thus offers great opportunity to further transform into different functionalities. However, the efficiency was lower even with high catalyst loading (entry 8). Other stronger electron-withdrawing groups, such as nitro and CN, completely shut down the transformation. Aliphatic nitriles and guanine derivatives were not fit for this transformation (entry 9). No observation of the desired product **1k** from *N*′-phenylated *N*-phenylbenzimidamide **2k** indicated that both free N–H groups are necessary for this process.

Different aniline derivatives were also surveyed (Table 3). Similarly, electron-rich functionalities were beneficial for

Table 1. Phenylation of **1a** under different conditions.[a]



	Cat. (10 mol%)	[O] (1.0 equiv)[b]	Additive (20 mol%)	Solvent	**2a** [%][c]
1	None	$Cu(OAc)_2/O_2$	TMTU	NMP	15
2	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	TMTU	NMP	16
3	$Pd(OTFA)_2$	$Cu(OAc)_2/O_2$	TMTU	NMP	29
4	$[PdCl_2(CH_3CN)_2]$	$Cu(OAc)_2/O_2$	TMTU	NMP	37
5	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	TMTU	NMP	60
6	$[PdCl_2(PhCN)_2]$	1,4-quinone	TMTU	NMP	<5
7	$[PdCl_2(PhCN)_2]$	oxone	TMTU	NMP	10
8	$[PdCl_2(PhCN)_2]$	$Cu(OTf)_2$	TMTU	NMP	21
9	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2$[e]	TMTU	NMP	7
10	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2$	TMTU	NMP	6
11	$[PdCl_2(PhCN)_2]$	O_2 (1 atm)	TMTU	NMP	<5
12	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2$[f]/O_2	TMTU	NMP	58
13	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	none	NMP	30
14	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	TMTU	*s*BuOH	<5
15	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	TMTU	toluene	<5
16	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	TMTU	CH_3CN	24
17	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	TMTU	DMF	45
18	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	TMTU	DMA	26
19	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	None	DMSO	42
20[d]	$[PdCl_2(PhCN)_2]$	$Cu(OAc)_2/O_2$	TMTU	DMSO	68

[a] The reactions were carried out in 0.5 mmol scale of **1a** in the presence of the proper catalyst in 2 mL of different solvents. [b] The pressure of dioxygen is 1 atm. [c] Isolated yields. [d] The product contained a small amount of dimethylsufone, which could not be separated with general methods. [e] 2 equiv. [f] 0.5 equiv.

Table 2. Selective imidazolation of substituted *N*-arylimidamides.[a]

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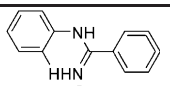
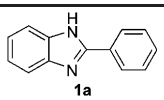
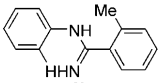
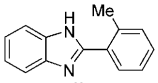
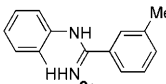
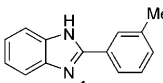
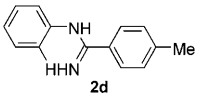
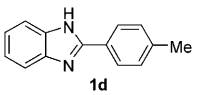
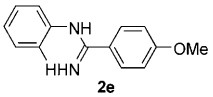
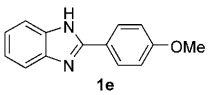
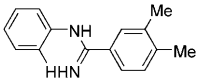
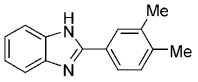
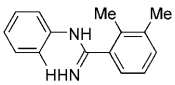
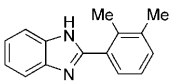
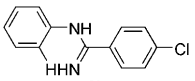
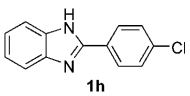
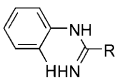
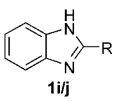
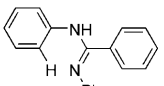
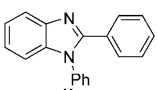
1			60
2			71
3			59
4[c]			64
5[c]			75
6[c]			63
7[c]			72
8[d]			40
9			0[e]
10			0

[a] All the reactions were carried out under the following reaction conditions: **2** (0.5 mmol), $[PdCl_2(PhCN)_2]$ (10 mol%), TMTU (20 mol%), and $Cu(OAc)_2$ (0.5 mmol) in NMP (2 mL) under O_2 atmosphere (balloon pressure) at 100°C. [b] Isolated yields.[c] 80°C. [d] 20.0 mol% $Pd(PhCN)_2Cl_2$ was used. [e] R = Me, NHPh.

Table 3. Selective imidazolation of substituted *N*-arylimidamides.[a]

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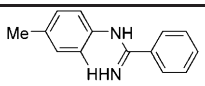
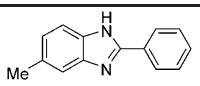
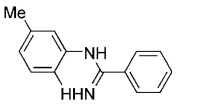
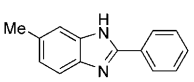
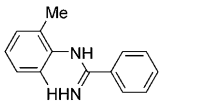
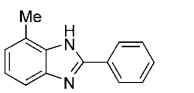
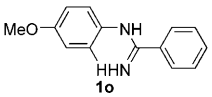
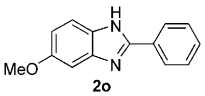
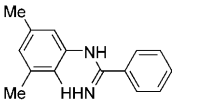
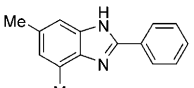
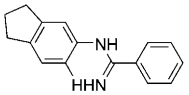
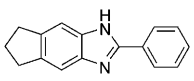
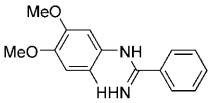
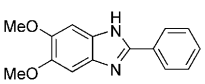
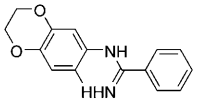
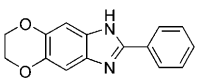
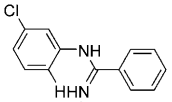
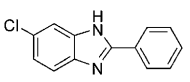
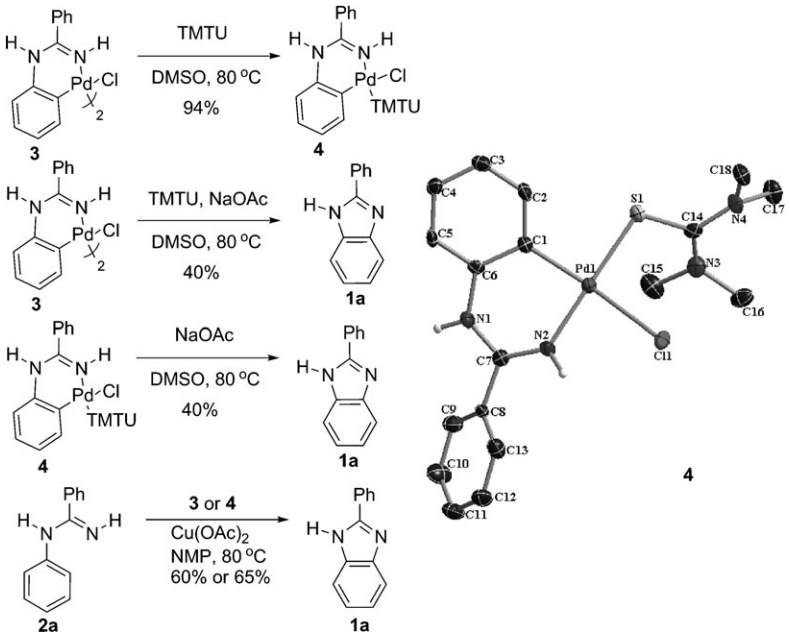
1			67
2			61[c]
3			32
4[c]			60
5			68
6			62[c]
7[d]			65
8[d]			53
9			40(1:1)

[a] All the reactions were carried out under the following reaction conditions: **1** (0.5 mmol), $[PdCl_2(PhCN)_2]$ (10 mol%), TMTU (20 mol%), and $Cu(OAc)_2$ (0.5 mmol) in NMP (2 mL) under O_2 atmosphere (balloon pressure) at 100°C. [b] Isolated yields. [c] Four isomers were observed with the same molecular weight by GC. [d] The reactions were carried out at 80°C.

this transformation. In contrast, electron-deficient substituents made the reactions less effective, which may arise from the decreased electron density on phenyl ring. When the nitro group was introduced into *para*-position, this reaction was totally shut down. Interestingly, steric effect also play a vital role in controlling the reactivity. Both *para*- and *meta*-methylated substrates showed good reactivity, but the *ortho*-methylated substrate evidently influenced the efficiency (cf: entries 1–3). It is important to note that when substrates **1m** and **1q**, with methyl and a fused five-membered carbon ring substituents, respectively, were used, four isomers were observed by GC that may arise from both the regioselectivity of the C–N formation and the migration of C=N group (entries 2 and 6). Interestingly, when substrate **1r** with 5,6-dimethoxy groups was used, only one isomer was isolated in a good yield (entry 7). In comparison, two isomers of the products were isolated in 1:1 and 2:1 ratios, respectively, when **1s** and **1t** served as the substrates with *meta*-substituents, in which the less hindered *ortho*-position was preferred (entries 8 and 9). Similarly, the C–Cl group survived well (entry 9).

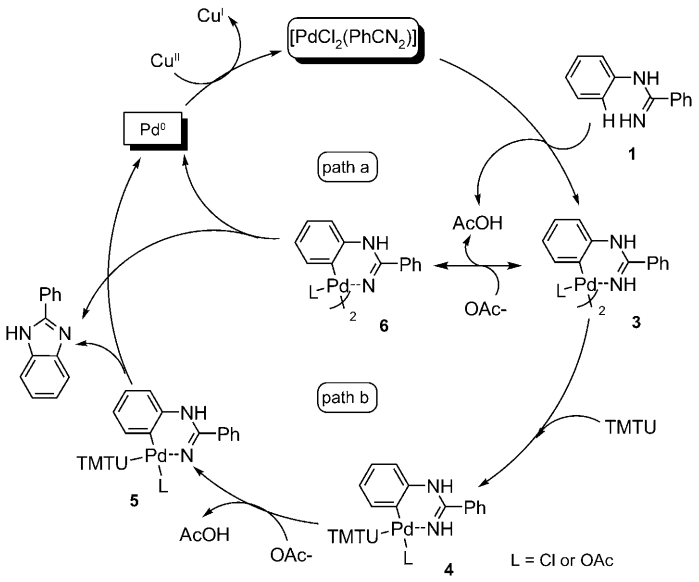
To clearly understand the mechanism, we further investigated the effect of TMTU (Scheme 3). The dimer of palladacycle **3** could be transformed into the palladacycle monomer **4** with TMTU as a ligand. This complex could be transformed into the desired product **1a** in a good efficiency in the presence of NaOAc as a base and in the absence of $Cu(OAc)_2$. In the presence of TMTU and NaOAc, palladacycle dimer **3** could be transformed into desired product in 40% isolated yield. Thus, TMTU may play an important role in



Scheme 3. Mechanistic studies for the direct imidation through palladacycles **3** and **4**.

promoting the reductive elimination. Moreover, both dimer and monomer could also be applied to this transformation as catalysts under standard conditions. This evidence offers strong support of the existence of palladacycles in the proposed catalytic cycle (Scheme 4).

On the basis of these preliminary studies, this transformation was hypothesized to occur through imino-group-directed *ortho*-cyclopalladation to produce the palladacycle **3**. After the decomposition of the dimeric palladacycle to produce the monomer **4** in the presence of TMTU, the acetate



Scheme 4. Plausible mechanism for the C–N formation of 1*H*-benzo[*d*]-imidazole through Pd-catalyzed C–H activation.

plays a role as a base to in removing the proton of the imine group to generate intermediate **5**. After the reductive elimination to yield the desired product **1**, a Pd^0 species is generated, which can be further oxidized to Pd^{II} to finish this catalytic cycle. The palladacycle dimer **3** may also go through the direct deprotonation and reductive elimination to finish this catalytic cycle according to its observed weak reactivity. The X-ray structures of intermediates **3** and **4** strongly supported these hypotheses. During this catalytic cycle, $Cu(OAc)_2$ was assumed to play dual roles both as a base in removing the proton of palladacycle monomer or dimer and an oxidant to oxidize Pd^0 to Pd^{II} to facilitate the catalytic cycle. The catalytic ability of $Cu(OAc)_2$ to produce the desired product could not be ruled out for this transformation. The observed electronic properties also support the features of the electrophilic attack pathway during the *ortho*-palladation. Further investigation to clearly understand the mechanism is underway.

We have developed a novel method to construct the core structure of 1*H*-benzo[*d*]imidazole through Pd^{II}-catalyzed C–H activation, starting from readily available *N*-phenylbenzimidamides under mild reaction conditions. This transformation has a broad substrate scope. Different functionalities survived well. Mechanistic studies strongly indicate that a Pd^{II} species plays an important role in facilitating the catalytic cycle via a palladacycle monomer or dimer as key intermediates. During this transformation, TMTU was used for the first time to promote the catalytic efficiency of the Pd^{II}-catalyzed C–H activation. This method offered the most straightforward pathway to diversify the benzimidamides.

Experimental Section

General: The boiling point of petroleum ether was between 60–90 °C. Silica gel (200–300 mesh) for purification was purchased from Qing Dao Hai Yang Chemical Industry Co. of China. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with Varian Mercury 300 spectrometer or at 400 MHz and 100.6 MHz, respectively, with Brucker ARX400 spectrometer. Mass spectrometric data were obtained using ZAB-HS mass spectrometer and GCT-MS Micromass UK. NMP and DMSO were dried over $CaSO_4$ and freshly distilled. $[PdCl_2(PhCN)_2]$, anhydrous $Cu(OAc)_2$, and TMTU were purchased from Acros Chemical and used without further purification.

General procedures for direct imidation to construct 1*H*-benzo[*d*]imidazole through Pd^{II}-catalyzed C–H activation: *N*-Phenylbenzimidamide (**1a**) or its derivatives (0.5 mmol, 1.0 equiv), $[PdCl_2(PhCN)_2]$ (0.05 mmol,

0.10 equiv), anhydrous $Cu(OAc)_2$ (0.5 mmol, 1.0 equiv), and TMTU (0.05 mmol, 0.10 equiv) were placed in a 25 mL Schlenck tube and dried NMP (2.0 mL) was added by syringe. The tube was sealed with a Teflon lined cap, and the reaction mixture was degassed and refilled with O_2 (repeated three times), then heated to 100 °C in an oil bath for 24 h. After the reaction was completed, saturated aq.Na_2CO_3 (5 mL) and ethyl acetate (10 mL) were added to the mixture. The dark solid was removed by filtration through Celite and the Celite bed was washed with 4×20 mL ethyl acetate. In most cases, the combined filtrate was washed with water (4×8 mL) and brine (10 mL). The organic phase was dried with Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography with a proper eluent. The purified material was dried under oil-pump vacuum.

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Keywords: C–H activation · C–N formation · homogeneous catalysis · palladium · thiourea

[1] For recent reviews of Pd- or Cu-catalyzed carbon–heteroatom bond-formation processes, see: a) L. Jiang, S. L. Buchwald in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **2004**, p. 699; b) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337; c) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; d) J. F. Hartwig, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley-Interscience, New York, **2002**, p. 1051; e) E. R. Strieter, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 939; *Angew. Chem. Int. Ed.* **2006**, *45*, 925; *Angew. Chem.* **2006**, *118*, 939; f) O. Kitagawa, M. Yoshikawa, H. Tanabe, T. Morita, M. Takahashi, Y. Dobashi, T. Taguchi, *J. Am. Chem. Soc.* **2006**, *128*, 12923; g) D. Zhu, R. Wang, J. Mao, L. Xu, F. Wu, B. Wan, *J. Mol. Catal. A* **2006**, *256*, 256.

[2] W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560.

[3] a) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048; b) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem.* **2005**, *117*, 2150; *Angew. Chem. Int. Ed.* **2005**, *44*, 2112.

[4] G. Brasche, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 1958; *Angew. Chem. Int. Ed.* **2008**, *47*, 1932.

[5] For reviews, see: a) M. Kataoka, M. Tatsuta, K. Yasoshima, T. Yura, K. Urbahns, A. Kiba, N. Yamamoto, J. B. Gupta, K. Hashimoto, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 805; b) M. Sabat, J. C. L. M. J. Vanrens, T. A. Brugel, J. Maier, A. Golebiowski, B. De, V. Easwaran, L. C. Hsieh, R. L. Walter, M. J. Mekel, A. Evdokimov, M. J. Janusz, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5973; c) R. B. Baudy, H. Fletcher III, J. P. Yardley, M. M. Zaleska, D. R. Bramlett, R. P. Tasse, D. M. Kowal, A. H. Katz, J. A. Moyer, M. Abou-Gharbia, *J. Med. Chem.* **2001**, *44*, 1516; d) H. Zarrinmayeh, A. M. Nunes, P. L. Ornstein, D. M. Zimmerman, M. B. Arnold, D. A. Schober, S. L. Gackenheimer, R. F. Bruns, P. A. Hipskind, T. C. Britton, B. E. Cantrell, D. R. Gehlert, *J. Med. Chem.* **1998**, *41*, 2709.

[6] a) M. R. Grimmett, *Imidazole and Benzimidazole Synthesis Best Synthetic Methods* (Ed.: O. Meth-Cohn), Academic Press, London, **1997**; b) D. Yang, D. Fokas, J. Li, L. Yu, C. M. Baldino, *Synthesis* **2005**, 47–56, and references therein; c) W. J. Ebenezer, M. G. Hutchings, K. Jones, D. A. Lambert, I. Watt, *Tetrahedron Lett.* **2007**, *48*, 1641.

[7] a) B. L. Zou, Q. L. Yuan, D. W. Ma, *Angew. Chem.* **2007**, *119*, 2652; *Angew. Chem. Int. Ed.* **2007**, *46*, 2598; b) N. Zheng, K. W. Anderson, X. H. Huang, H. N. Nguyen, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 7653; *Angew. Chem. Int. Ed.* **2007**, *46*, 7509.

[8] X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 7416.

[9] a) K. Pan, M. K. Scott, D. H. S. Lee, L. J. Fitzpatrick, J. J. Crooke, R. A. Rivero, D. I. Rosenthal, A. H. Vaidya, B. Zhao, A. B. Reitz, *Bioorg. Med. Chem.* **2003**, *11*, 185, and references therein; b) J. H. M. Lange, H. H. van Stuivenberg, H. K. A. C. Coolen, T. J. P. Adolfs, A. C. McCreary, H. G. Keizer, H. C. Wals, W. Veerman, A. J. M. Borst, W. de Looff, P. C. Verveer, C. G. Kruse, *J. Med. Chem.* **2005**, *48*, 1823.

[10] a) Y. Tang, L. Deng, Y. Zhang, G. Dong, J. Chen, Z. Yang, *Org. Lett.* **2005**, *7*, 1657; b) D. Yang, Y.-C. Chen, N.-Y. Zhu, *Org. Lett.* **2004**, *6*, 1577; c) Y. Nan, H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 297; d) B. Liang, J. Liu, Y.-X. Gao, K. Wongkhan, D.-X. Shu, Y. Lan, A. Li, A. S. Batsanov, J. A. H. Howard, T. B. Marder, J.-H. Chen, Z. Yang, *Organometallics* **2007**, *26*, 4756.

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