Heterocycles

DOI: 10.1002/anie.200802482

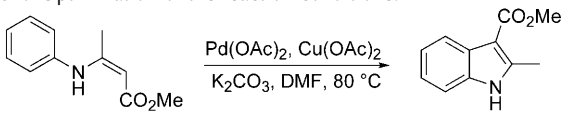
Palladium-Catalyzed Oxidative Cyclization of *N*-Aryl Enamines: From Anilines to Indoles**

*Sebastian Würtz, Souvik Rakshit, Julia J. Neumann, Thomas Dröge, and Frank Glorius**

The indole unit is one of the most abundant and relevant heterocycles in natural products and pharmaceuticals.[1] Despite the existence of numerous methods for the synthesis and derivatization of indoles,[2] the development of new, more efficient methods is of great importance. In this context, direct oxidative C–C coupling by the selective activation of two C–H bonds[3] is a promising synthetic strategy.[4,5] In contrast to established cross-coupling methods,[6] such as the Suzuki–Miyaura coupling, prefunctionalization of the reaction centers is not required. For example, electron-rich aniline substrates can be activated and functionalized by electrophilic aromatic palladation under acidic conditions to give indolequinones[7] or carbazoles.[8,9] However, the limited scope of these reactions, the frequent requirement of a stoichiometric amount of a palladium complex, and the low yields often observed limit the usefulness of these methods. Furthermore, simple non-annulated indoles could not be prepared under these acidic conditions.

Herein, we report an efficient synthesis of functionalized indoles from commercially available anilines by palladium-catalyzed, intramolecular oxidative coupling. As this cyclization does not proceed through electrophilic aromatic palladation, a large variety of anilines can be used in this reaction. Our investigation commenced with the cyclization of methyl (*Z*)-3-(phenylamino)but-2-enoate (**1a**) to give the corresponding indole **2a**. In experiments to optimize the reaction, the best results were obtained with a catalytic amount of $Pd(OAc)_2$, $Cu(OAc)_2$ as the oxidant, and K_2CO_3 as the base in DMF (Table 1, entry 1). Under these conditions, conversion was complete within 3 h at 80 °C (72 % yield of the isolated product), or within less than 15 min at 140 °C, even when only 5 mol % of $Pd(OAc)_2$ was used (not shown). Variation of the oxidant (Table 1, entries 3–6), the base (Table 1, entries 7 and 8), or the solvent (Table 1, entries 9–11) led to a decrease in the yield. The use of acetic acid as the solvent resulted in the rapid decomposition of the substrate and therefore no product formation (Table 1, entry 11). The results with $Pd(TFA)_2$ (TFA = trifluoroacetate) were similar to those observed under the optimal conditions (Table 1, entry 12), whereas the addition of PPh_3 resulted in the formation of a less active catalyst (Table 1, entry 13). Interestingly, chloride anions do not influence the reaction at all (Table 1, entry 14).[10]

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



1a "standard conditions" **2a**

Entry	Variation from the "standard conditions"	Yield[b] [%]
1	–	80 (72)[c]
2	no $Pd(OAc)_2$	< 5
3	Ag_2CO_3 instead of $Cu(OAc)_2$	23
4	benzoquinone instead of $Cu(OAc)_2$	< 5
5	benzoquinone[d]	60
6	$Cu(OAc)_2$ (2.1 equiv)	47
7	Cs_2CO_3 instead of K_2CO_3	64
8	no K_2CO_3	62
9	toluene instead of DMF	< 5
10	toluene instead of DMF, 110 °C	32
11	HOAc instead of DMF	< 5
12	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	75
13	PPh_3[d]	41
14	NaCl[e]	80

[a] Standard reaction conditions: **1a** (0.25 mmol), $Cu(OAc)_2$ (0.75 mmol), K_2CO_3 (0.75 mmol), $Pd(OAc)_2$ (10 mol %), DMF (3 mL), 80 °C, 14 h. [b] The yield was determined by GC. [c] The yield of the isolated product is given in brackets. [d] Included as an additive (20 mol %). [e] Included as an additive (50 mol %). DMF = *N*,*N*-dimethylformamide.

A great variety of substituted anilines can be transformed into the corresponding indoles under the optimized reaction conditions (Table 2). In some cases, an increased reaction temperature (and, consequently, a shorter reaction time) led to higher yields. Substrates with a variety of electron-donating (Table 2, entries 2–8) and electron-withdrawing substituents (Table 2, entries 9–19) were converted directly into the indole products, which are versatile building blocks for subsequent synthetic modification, for example, through modern cross-coupling reactions (Table 2, entries 12–14).[11,12] The ability to vary the aniline moiety so broadly is a distinct advantage of this new indole synthesis.

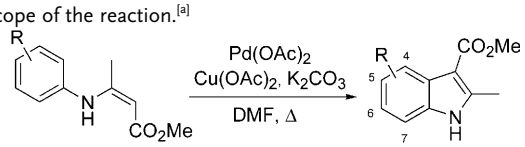
In the case of *meta*-substituted substrates **1**, two regioisomeric indole products **2** can be formed. Intriguingly, exclusive

[*] S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-833-3202
E-mail: glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/research/glorius/welcome.html

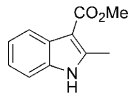
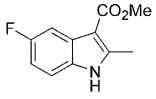
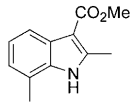
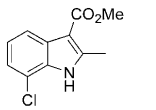
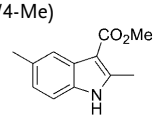
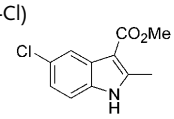
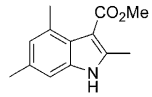
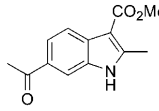
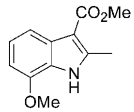
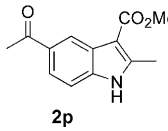
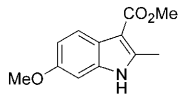
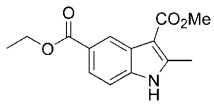
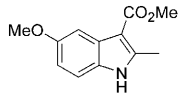
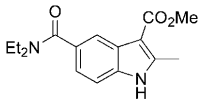
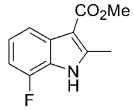
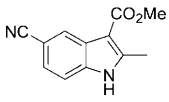
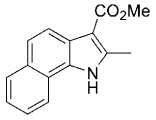
[**] We thank the Fonds der Chemischen Industrie, the Alfried Krupp von Bohlen und Halbach Foundation, the Deutsche Forschungsgemeinschaft, and the International Graduate School of Chemistry for generous financial support, Prof. Dr. M. Christl for mechanistic discussions, and Dr. H. Luftmann and Dr. K. Bergander for analytical support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802482.

Table 2: Scope of the reaction.[a]



1 **2**

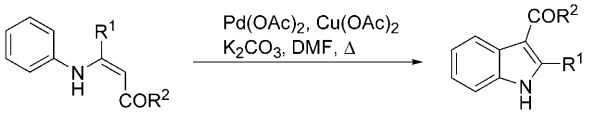
Entry	Product	Yield[b] [%]	Entry	Product	Yield[b] [%]
1[c]	 **2a**	72	11[d]	 **2k**	74
2[d]	 **2b**	82	12[c]	 **2l**	53
3[d] (6-Me/4-Me)	**2c**	68 (92:8[e])	13[c] (6-Cl/4-Cl)	**2m**	76 (88:12[e])
4[c]	 **2d**	72	14[c]	 **2n**	64
5[d]	 **2e**	62	15[f]	 **2o**	54 (>99:1[e])
6[f]	 **2f**	64	16[f]	 **2p**	52
7[f]	 **2g**	68 (>99:1[e])	17[f]	 **2q**	64
8[f]	 **2h**	64	18[f]	 **2r**	70
9[d]	 **2i**	78	19[f]	 **2s**	65
10[d] (6-F/4-F)	**2j**	74 (53:47[e])	20[c]	 **2t**	85 (>99:1[e])

[a] Reaction conditions: **1** (1 mmol), $Cu(OAc)_2$ (3 mmol), K_2CO_3 (3 mmol), $Pd(OAc)_2$ (10 mol%), DMF (12 mL), reaction time: 0.5 h at 140°C, 12–16 h at 80 or 110°C. [b] Yield of the isolated product. [c] The reaction was carried out at 80°C. [d] The reaction was carried out at 110°C. [e] The ratio of the regioisomers was determined by GC analysis. [f] The reaction was carried out at 140°C.

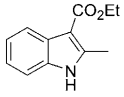
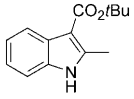
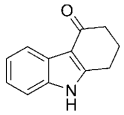
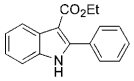
formation of the 6-substituted indole regioisomer was observed with both a mesomerically electron-donating methoxy and an electron-withdrawing acetyl substituent (Table 2, entries 7 and 15). The substrate derived from naphthylamine also underwent the desired reaction to give just one regioisomer of the product in good yield (85%; Table 2, entry 20). Whereas good selectivities were observed with methyl and chloro substituents (Table 2, entries 3 and 13), the presence of the small fluoro group led to the nonselective formation of the 4- and 6-substituted indole regioisomers (Table 2, entry 10). Evidently, the steric demand of the substituents is more important for selectivity in this transformation than their electronic character.

The enamine moiety was also varied successfully with the efficient formation of different carbonyl derivatives (Table 3, entries 1, 4, and 5), including a 2-aryl-substituted indole (Table 3, entry 6). We demonstrated on a 10 mmol scale that it is sufficient to use 2 mol% of the palladium catalyst and to use $Cu(OAc)_2$ hydrate as the oxidant (Table 3, entries 2 and 3). Furthermore, a one-pot reaction sequence enables rapid access to indoles from commercially available anilines.[13] Within minutes, aniline was condensed at room temperature with methyl acetoacetate in the presence of $InBr_3$ (1 mol%) without a solvent to give the corresponding enamine carboxylate,[14] which underwent

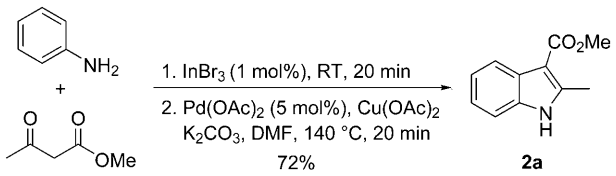
Table 3: Variation of the enamine unit.[a]



1 **2**

Entry	Product	Yield[b] [%]
1[c]	 **2u**	71
2[c,d]		70
3[e]		62
4[c]	 **2v**	79
5[f]	 **2w**	85
6[g]	 **2x**	68

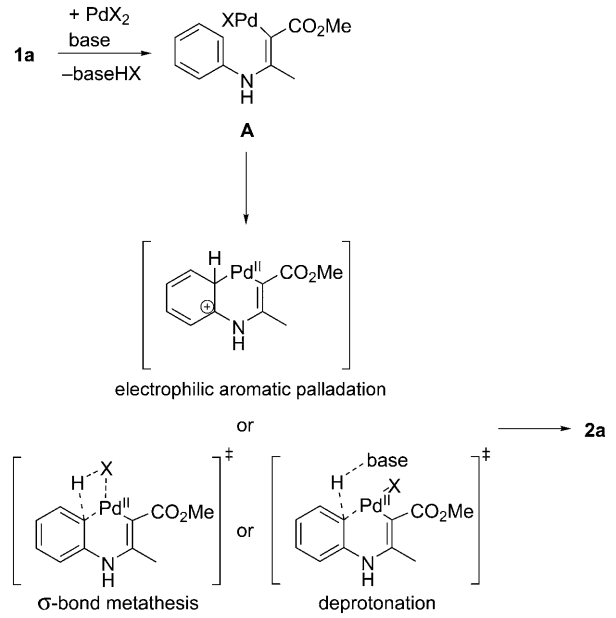
[a] Reaction conditions: **1** (1 mmol), $Cu(OAc)_2$ (3 mmol), K_2CO_3 (3 mmol), $Pd(OAc)_2$ (5–10 mol%), DMF (12 mL). [b] Yield of the isolated product. [c] $Pd(OAc)_2$ (5 mol%), 140°C, 30 min. [d] The reaction was carried out with $Cu(OAc)_2{\cdot}H_2O$ instead of $Cu(OAc)_2$. [e] Aniline **1** (10 mmol), $Cu(OAc)_2{\cdot}H_2O$ (30 mmol), K_2CO_3 (30 mmol), $Pd(OAc)_2$ (2 mol%), 140°C, 17 h. [f] $Pd(OAc)_2$ (10 mol%), 140°C, 24 h. [g] $Pd(OAc)_2$ (10 mol%), 180°C (microwave), 1 h.



Scheme 1. One-pot synthesis of indole **2a** from aniline and methyl acetoacetate.

subsequent cyclization under the standard conditions to give the desired indole product in 72% yield (Scheme 1).

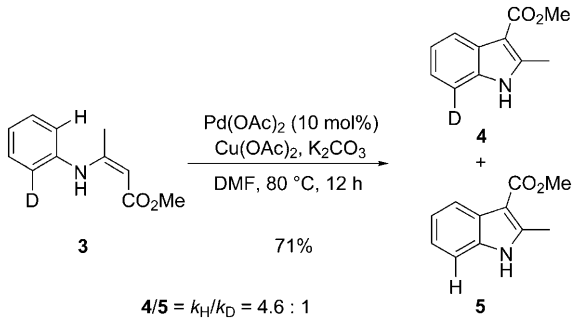
N-Aryl enamine carboxylates tend to react with electrophiles at the α C atom;[15] similar reactivity was also reported recently for a palladium-catalyzed coupling of enaminones with aryl borates.[16] Therefore, a plausible mechanism begins with an electrophilic palladation of the nucleophilic enamine,[17] followed by deprotonation (Scheme 2). The resulting palladium complex **A** is suitable for electrophilic aromatic palladation[18] or intramolecular C–H activation, such as



Scheme 2. Possible mechanistic pathways for the activation of the aromatic C–H bond of the aniline moiety.

σ-bond metathesis[19a,b] or base-assisted deprotonation.[19,20] Subsequent reductive elimination generates the indole product and a Pd^0 complex that can be reoxidized to the Pd^{II} complex by the oxidant $Cu(OAc)_2$.

The basic reaction conditions would lower the electrophilicity of a cationic $[PdX]^+$ species and thus render an electrophilic aromatic palladation mechanism unlikely.[5a] Furthermore, competition experiments with *para*-substituted substrates **1** showed that electron-donating groups in the *para* position slow down the transformation.[21] This observation is in agreement with a mechanism involving σ-bond metathesis or base-assisted deprotonation, but not with an electrophilic palladation (Scheme 2). The observation of an intramolecular kinetic isotope effect of $k_H/k_D = 4.6$ (Scheme 3) also supports



Scheme 3. Competition experiments for the determination of the kinetic isotope effect.

σ-bond metathesis and base-assisted deprotonation, but not an electrophilic aromatic palladation.

In summary, we have developed an efficient and broadly applicable direct oxidative synthesis of indoles from commercially available anilines. This transformation of anilines into indoles can also be carried out in a one-pot sequence. None of the substrates reported in this study were previously converted into indoles by cyclization. Thus, the method is an attractive alternative to Heck coupling reactions, which require the use of *ortho*-halogen-substituted anilines.[22] Initial mechanistic results speak unambiguously against an electrophilic aromatic palladation of the aniline ring and favor a σ-bond-metathesis or deprotonation pathway. The exploration of the use of air as an oxidant is under way, as well as further investigations into the mechanism and synthetic applications of this method.

Experimental Section

Representative procedure: Methyl (*Z*)-3-(phenylamino)but-2-enoate (**1a**; 191 mg, 1 mmol) was stirred in DMF (12 mL) together with $Pd(OAc)_2$ (22.5 mg, 10 mol%), $Cu(OAc)_2$ (545 mg, 3 mmol), and K_2CO_3 (415 mg, 3 mmol) at 80°C under an atmosphere of argon. After completion of the reaction (as indicated by TLC, GC, or GC–MS), the reaction mixture was cooled to room temperature, diluted with EtOAc (15 mL), and filtered through a short pad of silica, which was then washed with EtOAc (60 mL). Removal of the solvent in vacuo and purification of the residue by flash chromatography (SiO_2, pentane/EtOAc 5:1) provided indole **2a** (136 mg, 0.72 mmol, 72%) as an orange solid. The analytical data obtained were in agreement with the data reported in the literature.[23]

Received: May 27, 2008
Published online: August 13, 2008

Keywords: C–H activation · heterocycles · indoles · oxidation · palladium

[1] a) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278; b) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73; c) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761; for the physiological activity of indole derivatives, see: d) M. C. Van Zandt, M. L. Jones, D. E. Gunn, L. S. Geraci, J. H. Jones, D. R. Sawicki, J. Sredy, J. L. Jacot, A. T. DiCioccio, T. Petrova, A. Mitschler, A. D. Podjarny, *J. Med. Chem.* **2005**, *48*, 3141; for recent reports on the total synthesis of indole alkaloids, see: e) S. B. Herzon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 5342; f) P. S. Baran,

C. A. Guerrero, B. D. Hafensteiner, N. B. Ambhaikar, *Angew. Chem.* **2005**, *117*, 3960; *Angew. Chem. Int. Ed.* **2005**, *44*, 3892; g) T. Yamashita, N. Kawai, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2005**, *127*, 15038.

[2] For reviews on methods for the synthesis of indoles, see: a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; b) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045; see also the following reviews: c) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; d) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; for some recent indole syntheses, see: e) M. Shen, B. E. Leslie, T. G. Driver, *Angew. Chem.* **2008**, *120*, 5134; *Angew. Chem. Int. Ed.* **2008**, *47*, 5056; f) J. Takaya, S. Udagawa, H. Kusama, N. Iwasawa, *Angew. Chem.* **2008**, *120*, 4984; *Angew. Chem. Int. Ed.* **2008**, *47*, 4906; g) T. Pei, C.-y. Chen, P. G. Dormer, I. W. Davies, *Angew. Chem.* **2008**, *120*, 4299; *Angew. Chem. Int. Ed.* **2008**, *47*, 4231; h) K. Alex, A. Tillack, N. Schwarz, M. Beller, *Angew. Chem.* **2008**, *120*, 2337; *Angew. Chem. Int. Ed.* **2008**, *47*, 2304; i) O. Leogane, H. Lebel, *Angew. Chem.* **2008**, *120*, 356; *Angew. Chem. Int. Ed.* **2008**, *47*, 350.

[3] E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318.

[4] For the use of indole derivatives in cross-dehydrogenative coupling (CDC) reactions, see: a) T. Tsuchimoto, Y. Ozawa, R. Negoro, E. Shirakawa, Y. Kawakami, *Angew. Chem.* **2004**, *116*, 4327; *Angew. Chem. Int. Ed.* **2004**, *43*, 4231; b) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968; c) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578; d) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn, B. DeBoef, *Org. Lett.* **2007**, *9*, 3137; for a remarkable CDC of indoles with unfunctionalized benzene derivatives, see: e) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; f) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072.

[5] For CDCs of other substrates, see: a) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633; b) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 14047; c) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 11904; d) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586; e) M. Dams, D. E. De Vos, S. Celen, P. A. Jacobs, *Angew. Chem.* **2003**, *115*, 3636; *Angew. Chem. Int. Ed.* **2003**, *42*, 3512; f) K. Masui, H. Ikegami, A. Mori, *J. Am. Chem. Soc.* **2004**, *126*, 5074; g) Y. Zhang, C.-J. Li, *Angew. Chem.* **2006**, *118*, 1983; *Angew. Chem. Int. Ed.* **2006**, *45*, 1949; h) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 56; i) Z. Li, L. Cao, C.-J. Li, *Angew. Chem.* **2007**, *119*, 6625; *Angew. Chem. Int. Ed.* **2007**, *46*, 6505.

[6] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.

[7] a) B. Åkermark, J. D. Oslob, U. Heuschert, *Tetrahedron Lett.* **1995**, *36*, 1325; b) H. Hagelin, J. D. Oslob, B. Åkermark, *Chem. Eur. J.* **1999**, *5*, 2413; c) H.-J. Knölker, N. O'Sullivan, *Tetrahedron Lett.* **1994**, *35*, 1695; d) H.-J. Knölker, N. O'Sullivan, *Tetrahedron* **1994**, *50*, 10893; e) H.-J. Knölker, K. R. Reddy, A. Wagner, *Tetrahedron Lett.* **1998**, *39*, 8267; f) H.-J. Knölker, K. R. Reddy, *Synlett* **1999**, 596; g) S. Agarwal, S. Cämmerer, S. Filali, W. Fröhner, J. Knöll, M. P. Krahl, K. R. Reddy, H.-J. Knölker, *Curr. Org. Chem.* **2005**, *9*, 1601.

[8] a) B. Åkermark, L. Eberson, E. Jonsson, E. Pettersson, *J. Org. Chem.* **1975**, *40*, 1365; b) J. Knöll, H.-J. Knölker, *Synlett* **2006**, 651; c) M. P. Krahl, A. Jäger, T. Krause, H.-J. Knölker, *Org. Biomol. Chem.* **2006**, *4*, 3215; d) I. C. F. R. Ferreira, M.-J. R. P. Queiroz, G. Kirsch, *Tetrahedron* **2002**, *58*, 7943; e) T. Watanabe, S. Ueda, S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Chem. Commun.* **2007**, 4516.

[9] For a palladium-catalyzed cyclization of a single *N*-aryl-substituted (cyclic) enaminone under neutral conditions in 31% yield, see: a) H. Iida, Y. Yuasa, C. Kibayashi, *J. Org. Chem.* **1980**, *45*, 2938; for a two-step synthesis of indoles by anodic oxidation of an enaminone in 35% yield, and additional cyclizations, see: b) W. Eilenberg, H. J. Schäfer, *Tetrahedron Lett.* **1984**, *25*, 5023; for photochemical cyclizations for the synthesis of tricyclic ketoindoles, see: c) P.-J. Aragon, A.-D. Yapi, F. Pinguet, J.-M. Chezal, J.-C. Teulade, J.-P. Chapat, Y. Blache, *Chem. Pharm. Bull.* **2004**, *52*, 659; d) C. Tietcheu, C. Garcia, D. Gardette, D. Dugat, J.-C. Gramain, *J. Heterocycl. Chem.* **2002**, *39*, 965.

[10] NaCl was reported to inhibit oxidative Heck reactions; therefore, a different reaction mechanism appears to operate in our oxidative cyclization.[5d]

[11] For Suzuki–Miyaura reactions of chloroindoles, see: a) A. Fürstner, A. Leitner, *Synlett* **2001**, 290; b) N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1304; *Angew. Chem. Int. Ed.* **2006**, *45*, 1282.

[12] Bromo-substituted indoles can also be formed; however, a significant amount of the debrominated indole product is also obtained. The optimization of this reaction will be described at a later stage.

[13] As an example of the value of this method, we quote for one transformation the cost of purchasing the starting materials and the product in 99% purity from Sigma-Aldrich: aniline: 1 L/€24; ethyl acetoacetate: 1 kg/€37; ethyl-2-methylindole-3-carboxylate (**2u**): 1 g/€60.60.

[14] Z.-H. Zhang, L. Yin, Y.-M. Wang, *Adv. Synth. Catal.* **2006**, *348*, 184.

[15] a) M. E. F. Braibante, H. T. S. Braibante, C. C. Costa, D. B. Martins, *Tetrahedron Lett.* **2002**, *43*, 8079; b) M. E. F. Braibante, H. S. Braibante, L. Missio, A. Andricopulo, *Synthesis* **1994**, 898.

[16] H. Ge, M. J. Niphakis, G. I. Georg, *J. Am. Chem. Soc.* **2008**, *130*, 3708.

[17] An initial olefin–palladium π complex should also be considered; see: F. Glorius, *Angew. Chem.* **2004**, *116*, 3444; *Angew. Chem. Int. Ed.* **2004**, *43*, 3364, and references therein.

[18] A. M. Echavarren, B. Gómez-Lor, J. J. González, Ó. de Frutos, *Synlett* **2003**, 585.

[19] a) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066; b) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880; c) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496.

[20] Some alternative, though less likely mechanisms, may be considered; for a Heck carbopalladation, see: a) C. C. Hughes, D. Trauner, *Angew. Chem.* **2002**, *114*, 1639; *Angew. Chem. Int. Ed.* **2002**, *41*, 1569; b) B. Glover, K. A. Harvey, B. Liu, M. J. Sharp, M. F. Tymoschenko, *Org. Lett.* **2003**, *5*, 301; for an oxidative addition to a C–H bond to give a Pd^{IV} intermediate, see: c) A. J. Mota, A. Dedieu, C. Bour, J. Suffert, *J. Am. Chem. Soc.* **2005**, *127*, 7171; for a π,η^1 interaction of an aromatic ring with a Pd^{II} species, see: d) J. Cámpora, E. Gutiérrez-Puebla, J. A. López, A. Monge, P. Palma, D. del Río, E. Carmona, *Angew. Chem.* **2001**, *113*, 3753; *Angew. Chem. Int. Ed.* **2001**, *40*, 3641.

[21] The following reactivity order was found for *para*-substituted aniline substrates: Cl > H ≈ Me > OMe. Details are provided in the Supporting Information.

[22] For examples, see: a) N. Lachance, M. April, M.-A. Joly, *Synthesis* **2005**, 2571; b) U. S. Sørensen, E. Pombo-Villar, *Helv. Chim. Acta* **2004**, *87*, 82; c) C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *62*, 2676.

[23] S. Tanimori, H. Ura, M. Kirihata, *Eur. J. Org. Chem.* **2007**, 3977.

