

Ruthenium-Catalyzed Direct C–H Bond Arylations of Heteroarenes

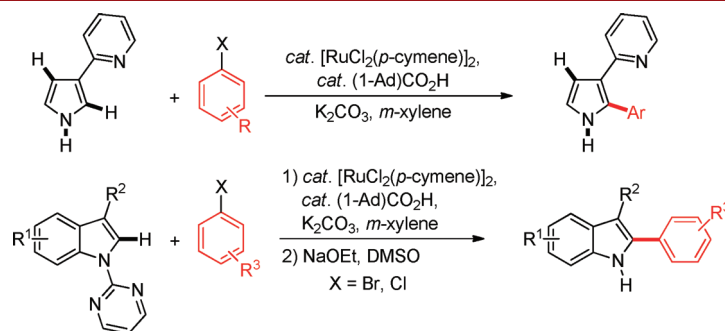
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ABSTRACT



Ruthenium-catalyzed C–H bond arylation of indoles, thiophenes, and pyrroles were accomplished in a highly chemo- and site-selective manner through the use of removable directing groups.

Heteroaromatic compounds represent indispensable structural motifs of *inter alia* functional materials, biologically active compounds, and natural products.^{1,2} The most economical approach to substituted heteroarenes arguably relies on transition-metal-catalyzed direct C–H

bond functionalizations,³ with remarkable progress being made in recent years through the use of palladium and rhodium complexes.^{3,4} On the contrary, ruthenium-catalyzed⁵ direct arylation of heteroarenes have to the best of our knowledge thus far not been accomplished. Recently, we introduced carboxylates as cocatalysts⁶ for efficient and robust ruthenium-catalyzed C–H bond arylation of arenes in various solvents.^{7,8} Mechanistic insight as to the rate-limiting step of carboxylate-assisted⁶ C–H bond functionalizations^{7,9} set the stage for the development of first ruthenium-catalyzed direct arylation of indoles,¹⁰ pyrroles, and thiophenes, on which we wish to report herein. An additional valuable asset of this strategy is represented by the unprecedented use of a removable directing group in ruthenium-catalyzed direct arylation of (hetero)arenes.¹¹

At the outset of our studies, we tested various cocatalysts in the direct arylation of 2-pyrimidyl-substituted indole **1a**, bearing a removable directing group (Table 1, and Table S-1 in the Supporting Information).¹² Thus, the synthesis of desired product **3a** occurred with remarkably high catalytic efficacy when using either sterically hindered secondary phosphine oxide (SPO)¹³ **4** (entry 3) or bulky carboxylic acid **5c** (entries 4–7). Interestingly, reactions proceeded well in aromatic solvents, while no conversion was observed in H₂O or frequently used 1-methyl-2-pyrrolidinone (NMP) as

(1) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003.

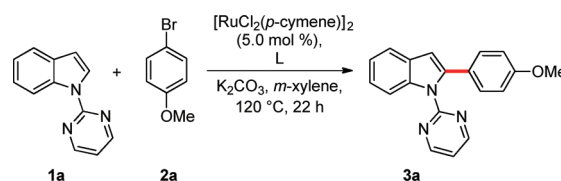
(2) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000.

(3) Select recent reviews on metal-catalyzed C–H bond functionalizations: (a) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780–1824. (b) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842–3844. (c) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725–748. (d) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (g) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (h) Jassar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654–2672. (i) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877. (j) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (k) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096–2098. (l) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (m) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109. (n) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (o) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (p) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (q) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (r) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (s) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (t) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238 and references cited therein.

the solvent (entries 8 and 9). As to the catalyst working mode,¹⁴ it is notable that well-defined ruthenium(II) carboxylate complex [Ru(O₂CMe)₂(*p*-cymene)] (**6**) turned out to be catalytically competent as well (entries 10 and 11).

With optimized reaction conditions in hand, we explored the scope of the *in situ* generated catalyst in direct arylations with differently substituted indole derivatives **1** (Scheme 1). The catalytic system proved broadly applicable and tolerated various valuable functional groups as well as additional heteroaromatic moieties. Decoration on

Table 1. Optimization Studies for the Direct Arylation of Indole **1a**^a



entry	L	yield
1	---	---
2	KOAc (30 mol %)	57%
3	(1-Ad) ₂ P(O)H (4) (10 mol %)	72%
4	MesCO ₂ H (5a) (30 mol %)	61%
5	<i>t</i> -BuCO ₂ H (5b) (30 mol %)	68%
6	(1-Ad)CO ₂ H (5c) (10 mol %)	71%
7	(1-Ad)CO ₂ H (5c) (30 mol %)	84%
8	(1-Ad)CO ₂ H (5c) (30 mol %)	--- ^b
9	(1-Ad)CO ₂ H (5c) (30 mol %)	--- ^c
10	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)] ^d (6) (5.0 mol %)	78%
11	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)] ^d (6) (2.0 mol %)	51%

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), [RuCl₂(*p*-cymene)]₂ (2.5 mol %), L, *m*-xylene (2.0 mL), 120 °C, 22 h, yields of isolated products. ^b In NMP (2.0 mL). ^c With H₂O (2.0 mL). ^d Instead of [RuCl₂(*p*-cymene)]₂.

the indole backbone was not detrimental to catalytic efficacy, which even allowed for high-yielding direct arylations of sterically demanding 1,3-disubstituted indoles. However, lower yields of isolated products **3** were obtained when using *ortho*-substituted aryl halides. With respect to the preparation of bioactive compounds it is noteworthy that the high catalytic activity set the stage for direct C—H

(11) For remarkable progress in palladium-catalyzed C—H bond functionalizations through the use of removable directing groups, see: (a) Garc  a-Rubia, A.; Fern  ndez-Ib    ez, M.   .; Array  s, R. G.; Carretero, J. C. *Chem.—Eur. J.* **2011**, *13*, 3567–3570. (b) Dudnik, A. S.; Chernyak, N.; Huang, C.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 8729–8732. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972. (d) Garcia-Rubia, A.; Urones, B.; Gomez Arrayas, R.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 9676–9685. (e) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270–8272. (f) Garcia-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511–6515. (g) Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2009**, *131*, 10844–10845. For examples of oxidative C—H bond functionalizations of saturated, non-aromatic heterocycles using boron-based reagents, see: (h) Prokopcov  , H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; van der Veken, B.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2010**, *16*, 13063–13067. (i) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221 and references cited therein.

(12) Intermolecular competition experiments between 2-pyridyl-substituted benzene and *N*-2-pyridyl-substituted indole revealed the latter to be functionalized preferentially (ratio: 9/91; Scheme S-1 in the Supporting Information). Attempted ruthenium-catalyzed direct arylations of free (*NH*)-indole did not meet with success.

(13) Reviews: (a) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663. (b) Ackermann, L. *Synthesis* **2006**, 1557–1571.

(14) Reactions with isotopically labeled starting materials and intermolecular competition experiments suggested the C—H bond metalation to be reversible in nature (Schemes S-2 and S-3 in the Supporting Information).

(15) For palladium-catalyzed direct arylations of electron-deficient pyridines through chelation assistance, see: Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275–1277.

(4) For representative recent reports on transition-metal-catalyzed direct arylations of heteroarenes, see: (a) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387–2391. (b) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780–3783. (c) Wagner, A. M.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 288–291. (d) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 3308–3311. (e) So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem.—Eur. J.* **2011**, *17*, 761–765. (f) N  dres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471–483. (g) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, 47, 430–432. (h) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946–8949. (i) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196. (j) Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 7863–7868. (k) Ackermann, L.; Jeyachandran, R.; Potukuchi, H. K.; Novak, P.; Buttner, L. *Org. Lett.* **2010**, *12*, 2056–2059. (l) Roy, D.; Mom, S.; Beaup  rin, M.; Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6650–6654. (m) Yagoubi, M.; Cruz, A. C. F.; Nichols, P. L.; Elliott, R. L.; Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 7958–7962. (n) Ackermann, L.; Barf  sser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724–726. (o) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674–3675. (p) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202–2205. (q) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8935–8939. (r) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070–12071. (s) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306. (t) Ackermann, L.; Barf  sser, S. *Synlett* **2009**, 808–812. (u) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473–1476. (v) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926–14927. (w) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748. (x) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996–8000. (y) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405. (z) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973 and references cited therein.

(5) (a) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229. (b) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413.

(6) A review: Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345.

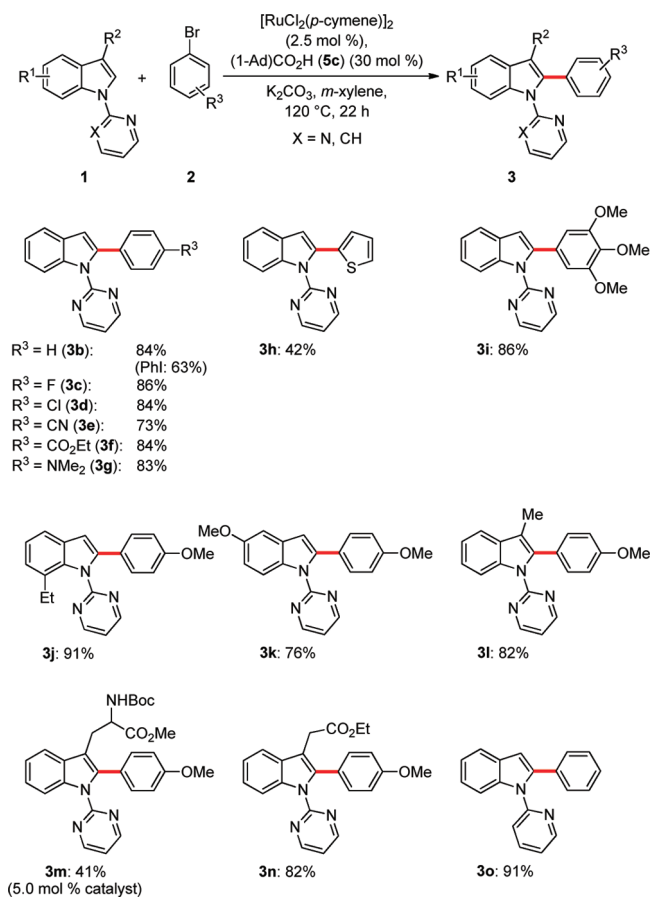
(7) (a) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035. (b) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5045. (c) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302.

(8) For representative subsequent contributions, see: Direct alkylations: (a) Ackermann, L.; Nov  k, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (b) Ackermann, L.; Nov  k, P. *Org. Lett.* **2009**, *11*, 4966–4969. An elegant application on scale: (c) Ouellet, S. G.; Roy, A.; Molinaro, C.; Angellaud, R.; Marcoux, J.-F.; O’Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 1436–1439. With H₂O: (d) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629–6632. See also: (e) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (f) Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem* **2009**, *546*–549. (g) Oi, S.; Funayama, R.; Hattori, T.; Inoue, Y. *Tetrahedron* **2008**, *64*, 6051–6059.

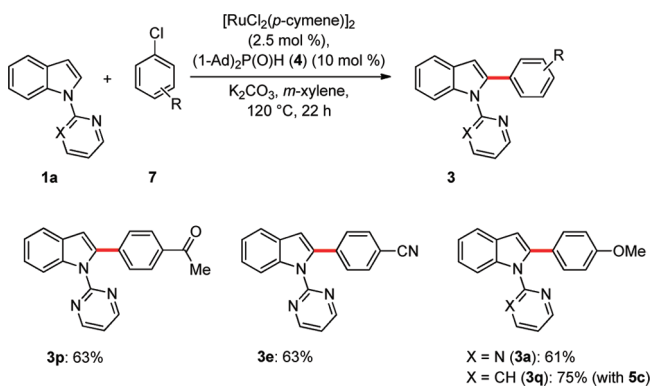
(9) See also: Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877.

(10) For select reviews on the preparation of indoles, see: (a) Cacchi, S.; Fabrizi, G.; Goggiani, A. *Org. Biomol. Chem.* **2011**, *9*, 641–652. (b) Kr  ger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153–2167. (c) Ackermann, L. *Synlett* **2007**, 507–526. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (f) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930 and references cited therein.

Scheme 1. Ruthenium-Catalyzed Direct Arylation of Indoles 1



Scheme 2. Direct Arylations of Indoles 1 with Aryl Chlorides 7



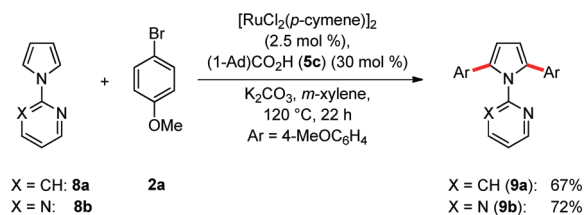
bond functionalizations on tryptophane derivatives. Furthermore, a 2-pyridyl substituent¹⁵ served as a powerful directing group as well.¹⁶

(16) Intermolecular competition experiments revealed that the directing group abilities exerted by 2-pyridyl- and 2-pyrimidyl-substituents are comparable (Scheme S-4 in the Supporting Information). For a pertinent report on the directing group abilities in *palladium*-catalyzed C–H bond functionalizations, see: Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285–13293.

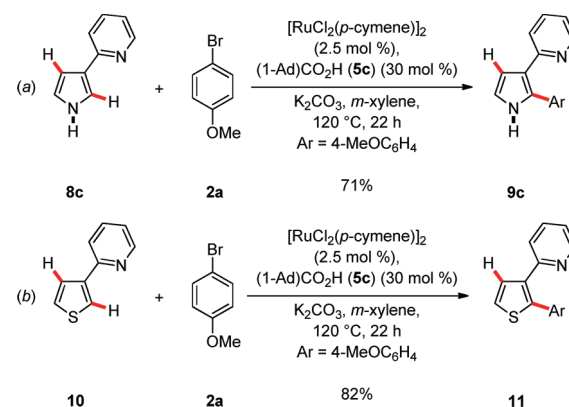
The base-assisted ruthenium-catalyzed direct arylation also proved applicable to the use of less expensive aryl chlorides **7**, with the most efficient catalysis being achieved with (1-Ad)₂P(O)H (**4**) as the preligand (Scheme 2; Table S-2 in the Supporting Information).

The protocol was not limited to indoles **1** as heteroaromatic substrates for C–H bond functionalizations. For instance, 2-pyridyl- or 2-pyrimidyl-substituted¹⁶ pyrroles **8a** and **8b** were efficiently converted to desired products **9a** and **9b**, respectively (Scheme 3).

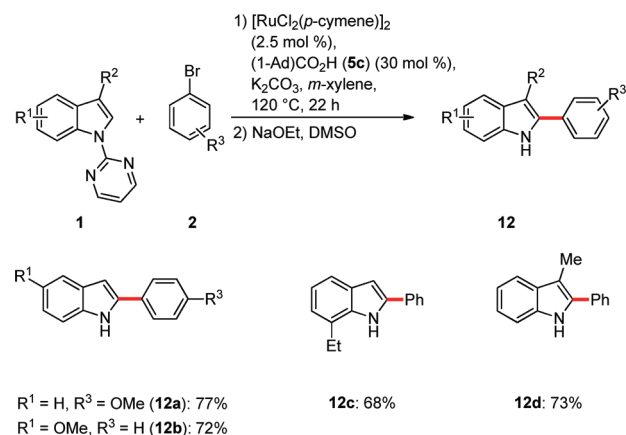
Scheme 3. Ruthenium-Catalyzed Direct Arylation of Pyrroles 8



Scheme 4. Chemo- and Site-Selective C–H Bond Functionalizations on Pyrrole 8c and Thiophene 10



Scheme 5. One-Pot Synthesis of Free (NH)-Indoles 12



The outstanding chemoselectivity of the optimized catalysts was illustrated by C–H bond functionalizations on unprotected pyrroles displaying acidic N–H functionalities (Scheme 4a). Interestingly, carboxylate-assisted direct arylations occurred with excellent site selectivity within intramolecular competition experiments. Thus, C-2-arylated pyrrole **9c** was generated as the sole product, as was thiophene **11** in the direct arylation of substrate **10** (Scheme 4b).

Finally, we took advantage of the removable directing group on indoles **1** for a high-yielding one-pot synthesis of free (*NH*)-indoles **12** (Scheme 5).

In conclusion, we have reported on the first ruthenium-catalyzed direct arylation of heteroarenes. Thus, carboxylic acids as cocatalysts enabled C–H bond functionalizations

on indoles, pyrroles, and thiophenes with excellent chemo- and site-selectivities. Furthermore, the unprecedented use of a removable directing group strategy in ruthenium-catalyzed direct arylations of (hetero)-arenes set the stage for the efficient synthesis of free (*NH*)-indoles.

Acknowledgment. Support by the DFG is gratefully acknowledged.

Supporting Information Available. Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.