ORGANIC LETTERS

2011
Vol. 13, No. 13
3332–3335

Ruthenium-Catalyzed Direct C−H Bond Arylations of Heteroarenes

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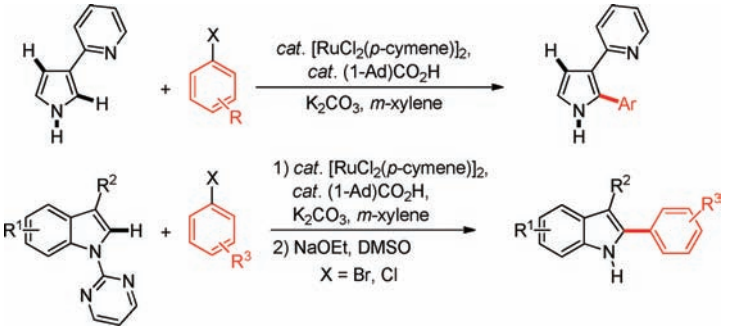
Received April 22, 2011

ABSTRACT



Ruthenium-catalyzed C−H bond arylations 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-catalyzed[5] direct arylations of heteroarenes have to the best of our knowledge thus far not been accomplished. Recently, we introduced carboxylates as cocatalysts[6] for efficient and robust ruthenium-catalyzed C−H bond arylations of arenes in various solvents.[7,8] Mechanistic insight as to the rate-limiting step of carboxylate-assisted[6] C−H bond functionalizations[7,9] set the stage for the development of first ruthenium-catalyzed direct arylations 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 arylations 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 H_2O or frequently used 1-methyl-2-pyrrolidinone (NMP) as

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

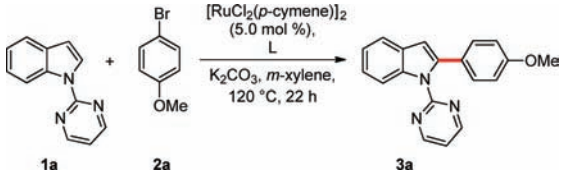
(3) Select recent reviews on metal-catalyzed C−H bond functionalizations: (a) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780–1824. (b) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842–3844. (c) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725–748. (d) Daugulis, O. *Top. 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) Jazzar, 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.

10.1021/ol2010648
Published on Web 06/06/2011

the solvent (entries 8 and 9). As to the catalyst working mode,[14] it is notable that well-defined ruthenium(II) carboxylate complex [$Ru(O_2CMes)_2$(*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 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

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



entry	L	yield
1	---	---
2	KOAc (30 mol %)	57%
3	$(1\text{-Ad})_2P(O)H$ (**4**) (10 mol %)	72%
4	$MesCO_2H$ (**5a**) (30 mol %)	61%
5	$t\text{-BuCO}_2H$ (**5b**) (30 mol %)	68%
6	$(1\text{-Ad})CO_2H$ (**5c**) (10 mol %)	71%
7	$(1\text{-Ad})CO_2H$ (**5c**) (30 mol %)	84%
8	$(1\text{-Ad})CO_2H$ (**5c**) (30 mol %)	---[b]
9	$(1\text{-Ad})CO_2H$ (**5c**) (30 mol %)	---[c]
10	$[Ru(O_2CMes)_2(p\text{-cymene})]$[d] (**6**) (5.0 mol %)	78%
11	$[Ru(O_2CMes)_2(p\text{-cymene})]$[d] (**6**) (2.0 mol %)	51%

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), $[RuCl_2(p\text{-cymene})]_2$ (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 H_2O (2.0 mL). [d] Instead of $[RuCl_2(p\text{-cymene})]_2$.

(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) Nadres, 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.; Beauperin, 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.; Barfüsser, 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.; Barfüsser, 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.

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(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.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (b) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966–4969. An elegant application on scale: (c) Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J.-F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 1436–1439. With H_2O: (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.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641–652. (b) Krüger, 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.

(11) For remarkable progress in palladium-catalyzed C−H bond functionalizations through the use of removable directing groups, see: (a) GarcÚa-Rubia, A.; Fernández-Ibáñez, M. Á.; Arrayás, 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) Prokopcová, 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.

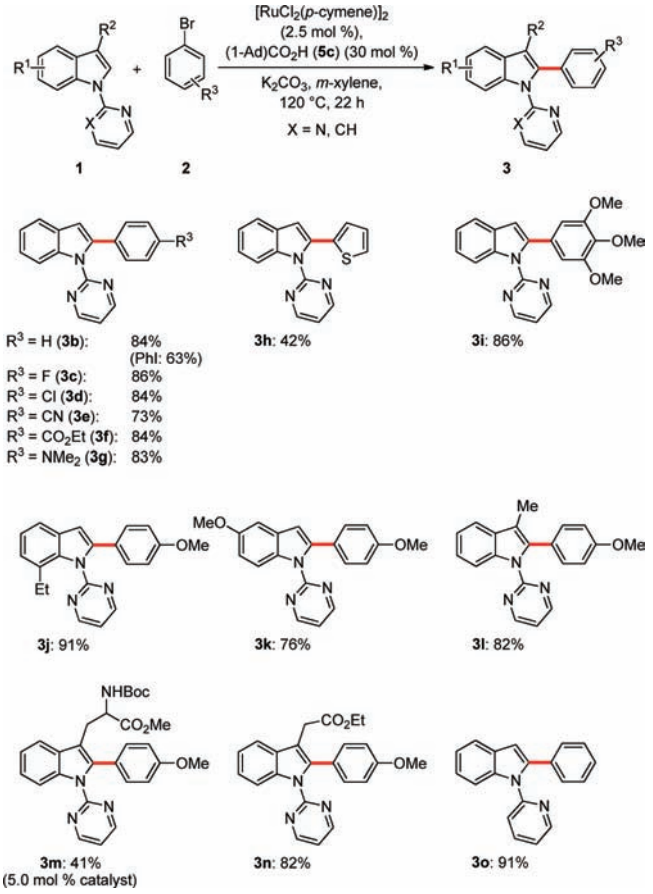
(12) Intermolecular competition experiments between 2-pyridyl-substituted benzene and *N*-2-pyridyl-substituted indole revealed the latter to be functionalized preferentially (ratio: 9/91; Scheme S-1 in the Supporting Information). Attempted ruthenium-catalyzed direct arylations of free (*NH*)-indole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

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

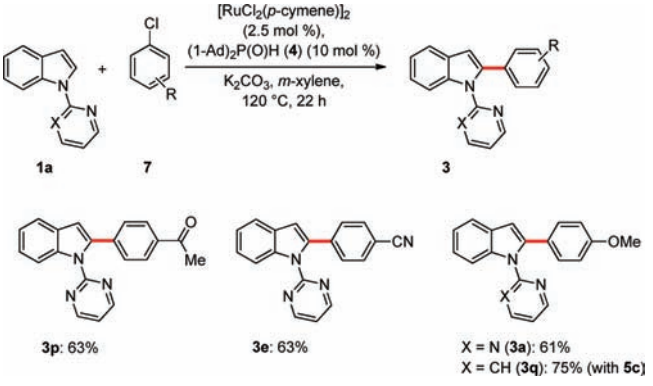
(14) Reactions with isotopically labeled starting materials and intermolecular competition experiments suggested the C−H bond metalation to be reversible in nature (Schemes S-2 and S-3 in the Supporting Information).

(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.

Scheme 1. Ruthenium-Catalyzed Direct Arylation of Indoles **1**



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



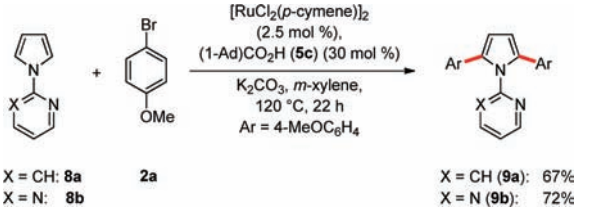
bond functionalizations on tryptophane derivatives. Furthermore, a 2-pyridyl substituent[15] served as a powerful directing group as well.[16]

(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.

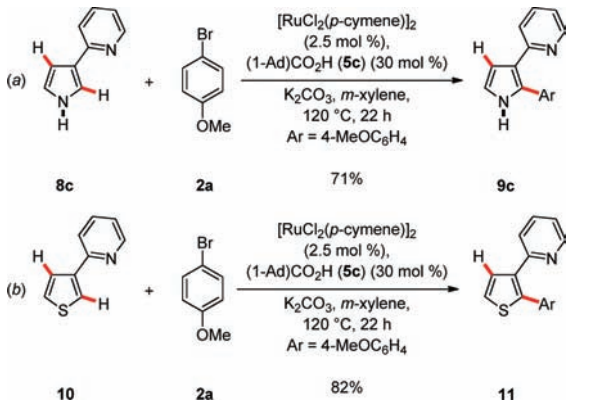
The base-assisted ruthenium-catalyzed direct arylation also proved applicable to the use of less expensive aryl chlorides **7**, with the most efficient catalysis being achieved with $(1\text{-Ad})_2\text{P(O)H}$ (**4**) as the preligand (Scheme 2; Table S-2 in the Supporting Information).

The protocol was not limited to indoles **1** as heteroaromatic substrates for C−H bond functionalizations. For instance, 2-pyridyl- or 2-pyrimidyl-substituted[16] pyrroles **8a** and **8b** were efficiently converted to desired products **9a** and **9b**, respectively (Scheme 3).

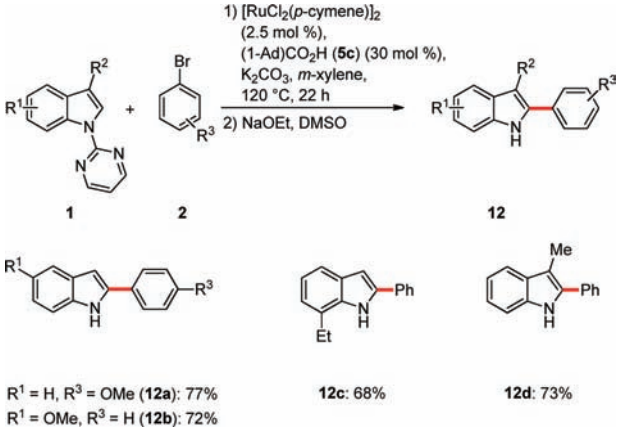
Scheme 3. Ruthenium-Catalyzed Direct Arylation of Pyrroles **8**



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 ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.