C–H Bond Activation

DOI: 10.1002/ange.201101943

Ruthenium-Catalyzed Oxidative Annulation by Cleavage of C–H/N–H Bonds**

Lutz Ackermann, Alexander V. Lygin, and Nora Hofmann*

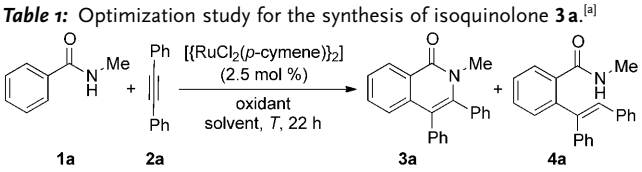
Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

Oxidative transition-metal-catalyzed C–H bond functionalizations[1] have attracted significant recent interest, because these methods avoid the multi-step preparation of preactivated starting materials, and hence allow for an overall streamlining of organic synthesis. Pioneering reports by the research groups of Miura and Satoh,[2] Fagnou,[3] and Jones[4] revealed that particularly rhodium catalysts enabled effective dehydrogenative annulation reactions of alkynes through chelation assistance,[5,6] which have set the stage for very recently developed rhodium-catalyzed isoquinolone[7] syntheses.[8] On the contrary, the use of less-expensive ruthenium[9] catalysts for oxidative annulations through cleavage of C–H bonds has thus far not been reported. During studies on oxidative ruthenium-catalyzed homodehydrogenative arylations,[10] we observed unprecedented ruthenium-catalyzed direct annulations of alkynes[11] through the chemo- and site-selective functionalization of both C–H and N–H bonds, and we wish to disclose our results herein.

At the outset of our studies, we explored the effect of different reaction parameters on the oxidative annulation of alkyne **2a** by amide **1a**, which included the use of representative ruthenium precursors, solvents, oxidants, and additives (Table 1, and Table S1 in the Supporting Information). Among a variety of ruthenium complexes, optimal yields of product **3a** were obtained with $[\{RuCl_2(p\text{-cymene})\}_2]$, along with $Cu(OAc)_2\cdot H_2O$ as the terminal oxidant, and *t*AmOH (*t*Am = *tert*-amyl) as the solvent. On the contrary, the use of silver(I) salts as stoichiometric oxidants resulted in decreased catalytic efficacy. As to the reaction mechanism (see below), the formation of compound **4a** in apolar solvents is noteworthy.[12]

With an optimized catalytic system in hand, we explored its scope in C–H bond functionalizations by employing differently substituted benzamides **1** (Scheme 1). Owing to its remarkable chemoselectivity the ruthenium catalyst proved tolerant of valuable electrophilic functional groups, such as fluoro, chloro, or ester substituents. Furthermore, amides **1** bearing different groups on the nitrogen atom,[13] such as *N*-alkyl, *N*-benzyl, or *N*-aryl derivatives, were efficiently reacted, with the latter being chemoselectively converted into isoquinolones **3k** and **3l**, without the formation of any indole[3] by-products.[14] Likewise, the successful use of a heteroaromatic benzamide turned out to be viable.

Table 1: Optimization study for the synthesis of isoquinolone **3a**.[a]



1a **2a** **3a** **4a**

Entry	Oxidant	Solvent	*T* [°C]	Conv. into **3a** [%][b]	Conv. into **4a** [%][b]
1	$Cu(OAc)_2\cdot H_2O$	*m*-xylene	120	58 (40)	19
2	–	*m*-xylene	120	0	–
3[c]	$Cu(OAc)_2\cdot H_2O$	*m*-xylene	120	0	–
4	$Cu(OAc)_2\cdot H_2O$	nBu_2O	120	32 (27)	40 (15)
5	$Cu(OAc)_2\cdot H_2O$	*t*AmOH	120	32	–
6	$Cu(OAc)_2\cdot H_2O$	*t*AmOH	100	61 (50)	–
7	$Cu(OAc)_2\cdot H_2O$	*t*AmOH	80	51	–
8	AgOAc	*t*AmOH	100	33	–
9	Ag_2CO_3	*t*AmOH	100	8	–
10[d]	$Cu(OAc)_2\cdot H_2O$	*t*AmOH	80	10	–
11[e]	$Cu(OAc)_2\cdot H_2O$	*t*AmOH	100	81 (62)	–
12[e,f]	$Cu(OAc)_2\cdot H_2O$	*t*AmOH	100	97 (76)	–

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (2.5 mol%), oxidant (2.0 equiv), solvent (2.0 mL). [b] Conversion determined by GC methods, and yields of isolated product in parentheses. [c] In the absence of $[\{RuCl_2(p\text{-cymene})\}_2]$. [d] Under air. [e] $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol%). [f] **1a** (0.5 mmol), **2a** (1.0 mmol).

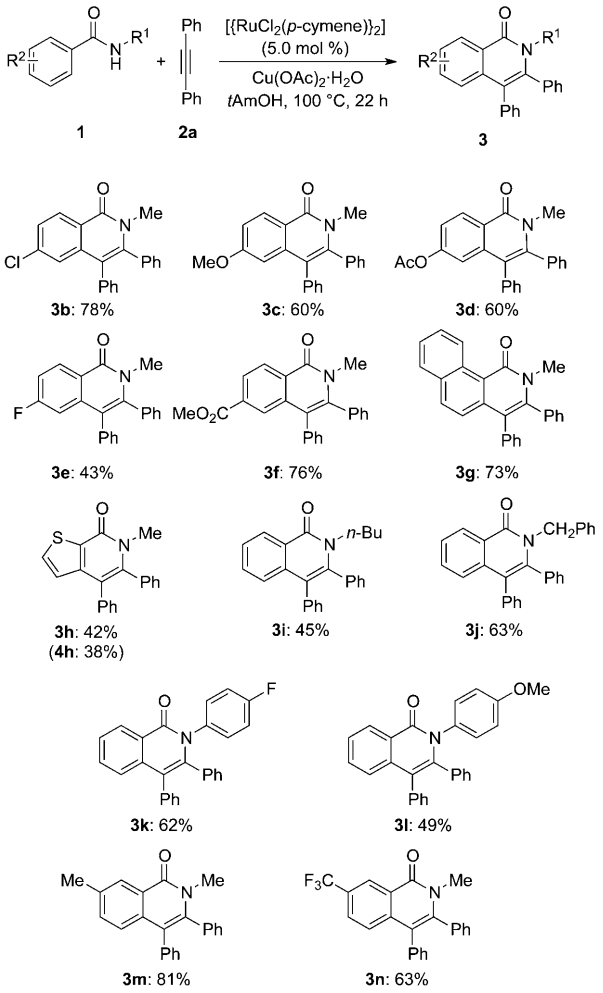
The catalytic system was not restricted to the use of tolane (**2a**), but also allowed for efficient oxidative annulations of aryl-, alkenyl- or alkyl-substituted alkynes **2** (Scheme 2). Importantly, the annulation process occurred with high regioselectivity even when using unsymetrically substituted aryl/alkyl or alkenyl/alkyl[6a] alkynes **2**.[15]

Given the remarkable activity of the novel catalytic system, we became interested in understanding its mode of action. Thus, intramolecular competition experiments with *meta*-substituted substrates were largely controlled by steric interactions, thus delivering isoquinolones **3m** and **3n** as the sole products (Scheme 1). In contrast, the use of substrates **1b** and **1c**, which have electronegative heteroatoms in *meta*-position, gave significant amounts of products **3w** and **3y**,[16] respectively, through C–H bond functionalizations at the 2-

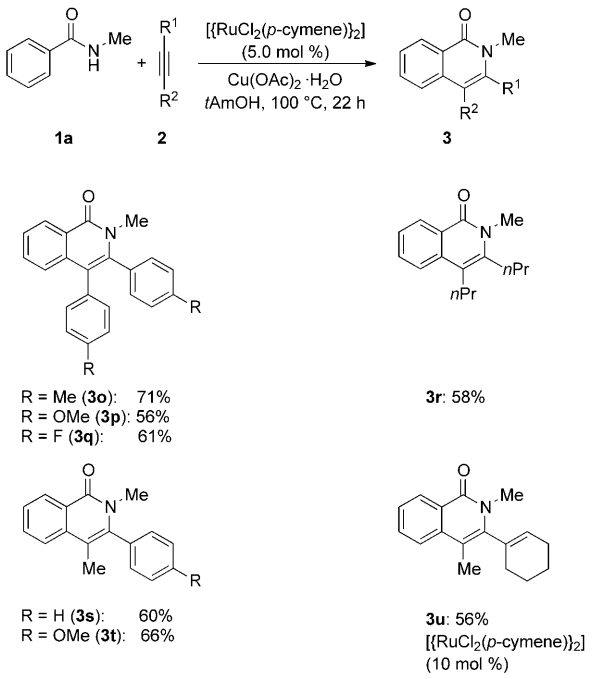
[*] Prof. Dr. L. Ackermann, Dr. A. V. Lygin, Dipl.-Chem. N. Hofmann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-39-6777
E-mail: lutz.ackermann@chemie.uni-goettingen.de
Homepage: http://www.org.chemie.uni-goettingen.de/ackermann/

[**] Support by the CaSuS PhD program (fellowship to N.H.), and the DFG is gratefully acknowledged.

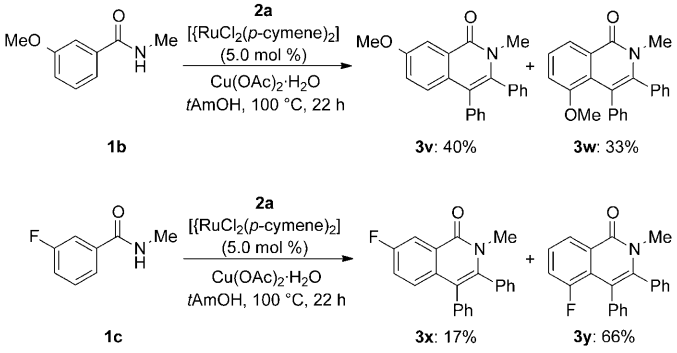
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101943.



Scheme 1. Scope of ruthenium-catalyzed oxidative annulation.



Scheme 2. Scope of the ruthenium-catalyzed oxidative annulation with alkynes **2**.



Scheme 3. Intramolecular competition experiments with *meta*-substituted amides.

position of the arenes (Scheme 3). These observations can be rationalized with the C–H bond acidity[17] or Ru–C bond stability[18,19] governing the site selectivity of the overall annulation process within a carboxylate-assisted[20] ruthenation manifold.

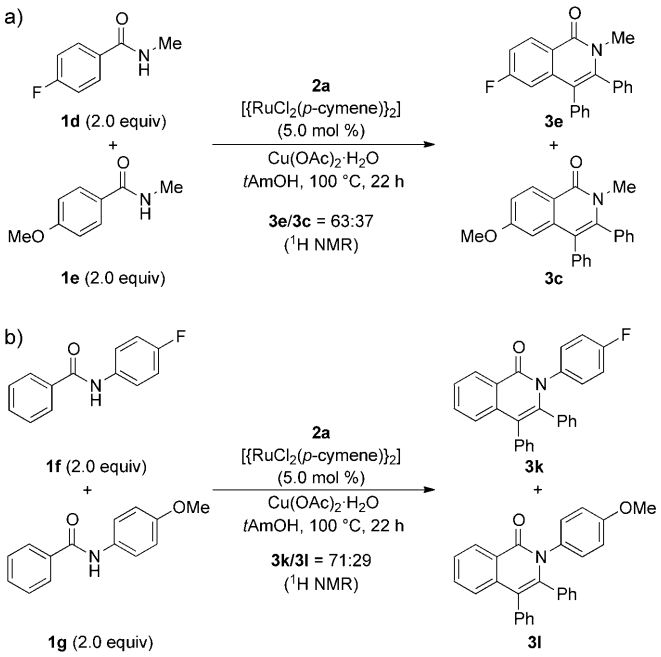
Moreover, intermolecular competition experiments revealed electron-deficient benzamides **1** to be functionalized preferentially, hence rendering an electrophilic C–H bond activation less likely to be operative (Scheme 4a). Further, benzamides **1** with less electron-rich nitrogen substituents were found to be more efficiently converted to the corresponding isoquinolones **3** (Scheme 4b).

Intermolecular competition experiments with differently substituted alkynes **2** showed that electron-deficient tolane derivatives reacted preferentially (Scheme 5), a notable difference to a rhodium-catalyzed oxidative annulation process.[8]

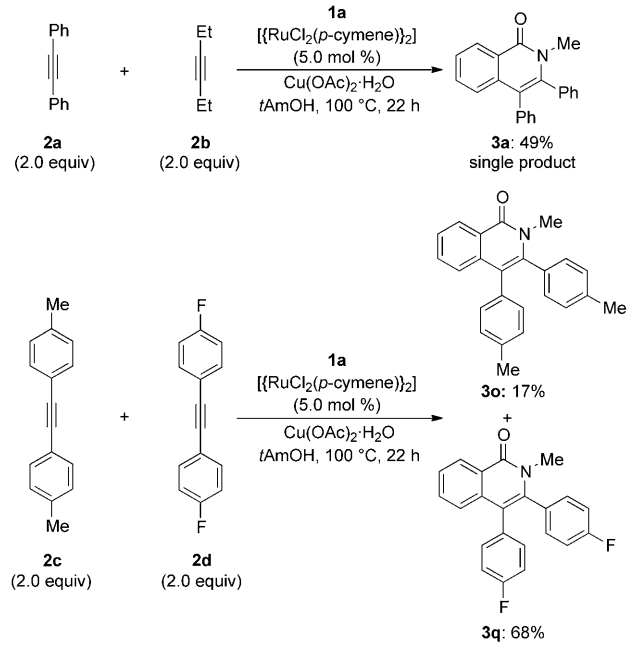
Finally, we performed studies with isotopically labeled solvents and substrates **1** (Scheme 6, and the Supporting Information). These experiments were suggestive of an irreversible C–H bond metalation with a kinetic isotope effect (KIE) of $k_H/k_D \approx 2.6$. A KIE of this magnitude is in good agreement with a concerted acetate-assisted metalation transition state.[20,21]

Based on our mechanistic studies we propose the ruthenium-catalyzed oxidative annulation to proceed by an initial intermolecular carboruthenation of alkyne **2** via rate-limiting acetate-assisted C–H bond ruthenation, and subsequent intramolecular oxidative C–N bond formation (Scheme 7).

In summary, we have developed the first ruthenium-catalyzed oxidative annulation reaction of alkynes, which gave efficient access to isoquinolones with ample scope. A valuable asset of the inexpensive catalytic system is represented by its remarkably high chemo- and regioselectivity. Mechanistic studies on this novel C–H/N–H bond-functionalization process provided strong evidence for a rate-limiting C–H bond metalation through carboxylate assistance, a striking difference to a rhodium-catalyzed isoquinolone

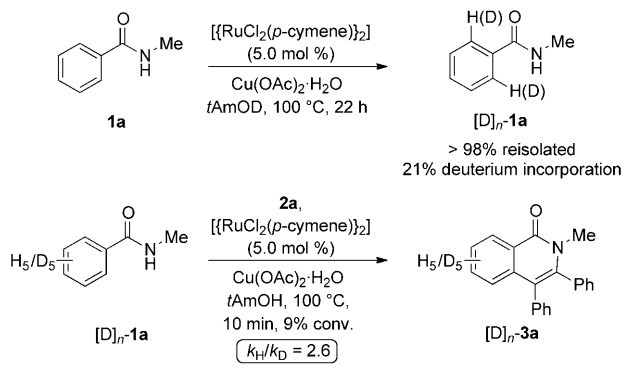


Scheme 4. Intermolecular competition experiments with benzamides **1**.

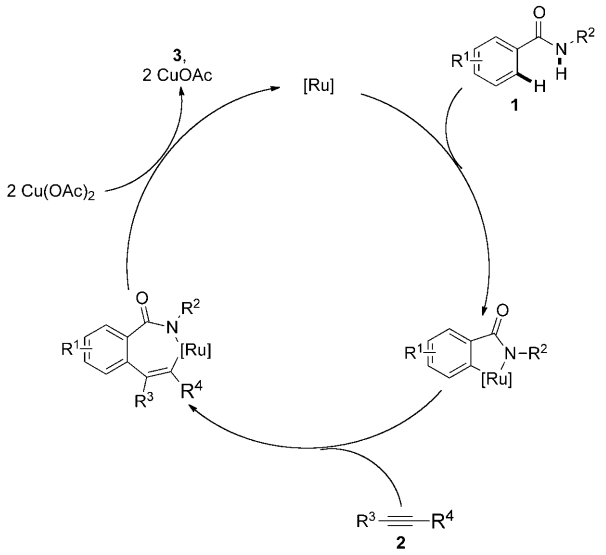


Scheme 5. Intermolecular competition experiments with alkynes **2**.

synthesis.[8a] Furthermore, it is noteworthy that the ruthenium catalyst converts electron-deficient alkynes with increased efficacy and leads to improved isolated yields when using *N*-benzyl-substituted benzamides as substrates. Further applications of ruthenium-catalyzed oxidative C–H bond functionalizations are ongoing in our laboratories, and will be reported in due course.



Scheme 6. Experiments with isotopically labeled compounds.



Scheme 7. Proposed catalytic cycle.

Experimental Section

Representative procedure for ruthenium-catalyzed oxidative annulation. Synthesis of **3a** (Table 1, entry 12): A mixture of **1a** (67.5 mg, 0.50 mmol), **2a** (178 mg, 1.00 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (15.3 mg, 5.0 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol) in *t*AmOH (2.0 mL) was stirred at 100 °C under nitrogen for 22 h. After cooling the reaction mixture to ambient temperature, it was diluted with aq NH_3 (75 mL, 1.0 wt%) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuum, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4:1) to yield **3a** as a colorless solid (118 mg, 76%).

Received: March 18, 2011
Revised: April 18, 2011
Published online: May 24, 2011

Keywords: annulation · C–H activation · heteroarenes · oxidation · ruthenium

[1] Select recent reviews on metal-catalyzed C–H bond functionalizations: a) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725–748; b) O.

Daugulis, *Top. Curr. Chem.* **2010**, *292*, 57 – 84; c) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677 – 685; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624 – 655; e) K. Fagnou, *Top. Curr. Chem.* **2010**, *292*, 35 – 56; f) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654 – 2672; g) A. Lei, W. Liu, C. Liu, M. Chen, *Dalton Trans.* **2010**, *39*, 10352 – 10361; h) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866 – 4877; i) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169; j) A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 2140 – 2142; *Angew. Chem. Int. Ed.* **2010**, *49*, 2096 – 2098; k) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242 – 3272; l) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087 – 4109; m) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem.* **2009**, *121*, 9976 – 10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792 – 9826; n) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196 – 5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094 – 5115; o) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874 – 5883; p) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074 – 1086; q) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013 – 3039; r) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200 – 205; s) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174 – 238, and references therein.

[2] a) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362 – 5367; b) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407 – 1409.

[3] D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474 – 16475.

[4] L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414 – 12419.

[5] Recent reviews: a) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212 – 11222; b) T. Satoh, M. Miura, *Synthesis* **2010**, 3395 – 3409.

[6] For important recent progress, see: [Rh]: a) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem.* **2011**, *123*, 1374 – 1377; *Angew. Chem. Int. Ed.* **2011**, *50*, 1338 – 1341; b) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326 – 18339; c) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585 – 9587; d) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068 – 2071; e) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050 – 12051; f) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem.* **2008**, *120*, 4083 – 4086; *Angew. Chem. Int. Ed.* **2008**, *47*, 4019 – 4022; [Cu]: g) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222 – 8225; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078 – 8081; [Pd]: h) J. Wu, X. Cui, X. Mi, Y. Li, Y. Wu, *Chem. Commun.* **2010**, *46*, 6771 – 6773; i) Z. Shi, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 8035 – 8038; *Angew. Chem. Int. Ed.* **2009**, *48*, 7895 – 7898, and references therein; for related studies, see: j) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676 – 3677; k) C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagne, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066 – 10067.

[7] For recent examples of metal-catalyzed isoquinolone syntheses, see: a) Y. Kajita, S. Matsubara, T. Kurahashi, *J. Am. Chem. Soc.* **2008**, *130*, 6058 – 6059; b) C.-C. Liu, K. Parthasarathy, C.-H. Cheng, *Org. Lett.* **2010**, *12*, 3518 – 3521, and references therein.

[8] a) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565 – 10569; b) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744 – 746; c) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487 – 7490; for an isohypsic approach, see: d) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908 – 6909; e) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449 – 6457.

[9] $[\{Cp^*RhCl_2\}_2]$: €2545 versus $[\{RuCl_2(p\text{-cymene})\}_2]$: €257 (5.0 g, Sigma–Aldrich, 17.03.2011). A review on ruthenium-catalyzed direct C–H bond arylations: L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010**, *292*, 211 – 229.

[10] L. Ackermann, P. Novák, R. Vicente, V. Pirovano, H. K. Potukuchi, *Synthesis* **2010**, 2245 – 2253.

[11] For a pioneering ruthenium-catalyzed cross-dehydrogenative coupling with alkenes, see: a) H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337 – 338; see also: b) T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 706 – 708.

[12] Independently prepared amide **4a** was not converted into isoquinolone **3a** under the optimized reaction conditions.

[13] The use of a primary amide as substrate yielded only trace amounts of polycyclic amides. For a recent rhodium-catalyzed transformation, see Ref. [8c].

[14] *ortho*-Methyl-substituted benzamide delivered the corresponding isoquinolone in 33% yield of isolated product.

[15] The use of a terminal alkyne provided only unsatisfactory results.

[16] For a related observation in rhodium-catalyzed oxidative coupling reactions, see: N. Umeda, K. Hirano, T. Satoh, N. Shibata, H. Sato, M. Miura, *J. Org. Chem.* **2011**, *76*, 13 – 24.

[17] K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568 – 1576.

[18] E. Clot, C. Megret, O. Eisenstein, R. N. Perutz, *J. Am. Chem. Soc.* **2009**, *131*, 7817 – 7827.

[19] D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749 – 823.

[20] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345, and references therein.

[21] A representative early example: A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky, *Dalton Trans.* **1985**, 2629 – 2638.

