Heterocycle Synthesis

International Edition: DOI: 10.1002/anie.201503997
German Edition: DOI: 10.1002/ange.201503997

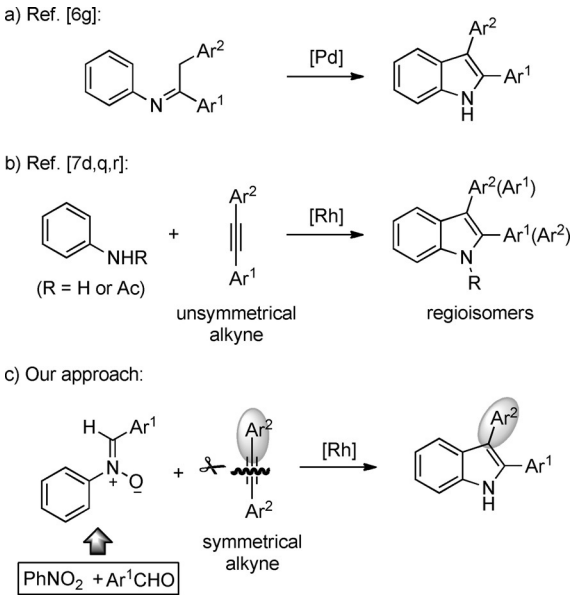
Rhodium-Catalyzed C–H Annulation of Nitrones with Alkynes: A Regiospecific Route to Unsymmetrical 2,3-Diaryl-Substituted Indoles**

Hao Yan, Haolong Wang, Xincheng Li, Xiaoyi Xin, Chunxiang Wang, and Boshun Wan**

Abstract: *The direct C–H annulation of anilines or related compounds with internal alkynes provides straightforward access to 2,3-disubstituted indole products. However, this transformation proceeds with poor regioselectivity in the synthesis of unsymmetrically 2,3-diaryl substituted indoles. Herein, we report the rhodium(III)-catalyzed C–H annulation of nitrones with symmetrical diaryl alkynes as an alternative method to prepare 2,3-diaryl-substituted N-unprotected indoles with two different aryl groups. One of the aryl substituents is derived from N=C-aryl ring of the nitrone and the other from the alkyne substrate, thus providing the indole products with exclusive regioselectivity.*

Indole motifs are present in a wide variety of natural products, pharmaceuticals, and agrochemicals.[1] Consequently, their preparation has drawn much attention, and a number of useful methods have been reported for the preparation of functionalized indoles.[2–5] More recently, transition-metal-catalyzed cross-dehydrogenative coupling (CDC) reactions[6] as well as directing-group-assisted intermolecular C–H annulation[7] and other methods[8–11] have emerged as powerful tools for their synthesis. Despite these impressive advances, the synthesis of unsymmetrical 2,3-diaryl-substituted indoles in a highly regioselective manner remains challenging.

Well-established methods exist for the preparation unsymmetrical 2,3-diaryl-substituted indoles from prefunctionalized reactants or by multistep procedures.[8b,f,i,11] However, C–H functionalization has been demonstrated to be a more versatile and efficient strategy for the synthesis of heterocycles.[12] For example, Yoshikai and co-workers[6g] reported a significant palladium-catalyzed intramolecular CDC reaction of *N*-aryl imines prepared from simple anilines and ketones (Scheme 1 a) in which the regioselectivity could be controlled perfectly by the ketone moiety. A more intriguing method is the direct and atom-economical C–H annulation of anilines (or anilides) with unsymmetrical diaryl alkynes (Scheme 1 b).[7d,q,r] However, the control of regioselectivity is still problematic in this type of annulation.



Scheme 1. Synthesis of unsymmetrically 2,3-diaryl substituted indoles by metal-catalyzed C–H annulation.

Previous studies revealed that electronic rather than steric effects of the diaryl alkyne substituents had a dominant effect on the regioselectivity.[7d,r] Therefore, it is difficult to predict the regioselectivity with unsymmetrical diaryl alkynes, although in some special cases excellent regioselectivity was observed.[7q] In this context, the reaction with symmetrical diaryl alkynes is more controllable. Recently, we observed C–H activation of the *N*-aryl ring of nitrones by a Rh^{III} intermediate generated in situ.[13] In connection with the challenges associated with the synthesis of unsymmetrically 2,3-diaryl substituted indoles, we envisioned that the C–H annulation of nitrones with *symmetrical* diaryl alkynes under Rh^{III} catalysis might provide a possibility to access indole products (Scheme 1 c). Nitrones for this reaction can be prepared from readily available nitroarenes and aromatic aldehydes.[14] The symmetrical alkyne acts as a one-carbon-atom unit through carbon–carbon triple-bond cleavage[15] to allow access to a broad range of unsymmetrical 2,3-diaryl-substituted N-unprotected[16] indoles with exclusive regioselectivity. Herein, we report our preliminary results.

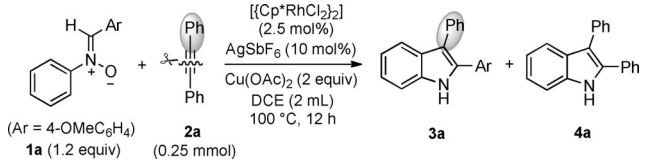
An initial study was carried out with nitrone **1a** and alkyne **2a** as model substrates in the presence of a Rh^{III} catalyst.[13] Gratifyingly, the unsymmetrical 2,3-diaryl-substituted indole **3a** was obtained in 43% yield, along with 2,3-diphenylindole (**4a**) and PhCHO as by-products (Table 1, entry 1). The structure of **3a** was confirmed unambiguously

[*] H. Yan, Dr. H. L. Wang, Dr. X. C. Li, Dr. X. Y. Xin, Dr. C. X. Wang, Prof. Dr. B. S. Wan
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
457 Zhongshan Road, Dalian 116023 (China)
E-mail: cxwang@dicp.ac.cn
bswan@dicp.ac.cn

[**] This research was supported by the NSFC (21372219).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503997.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

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

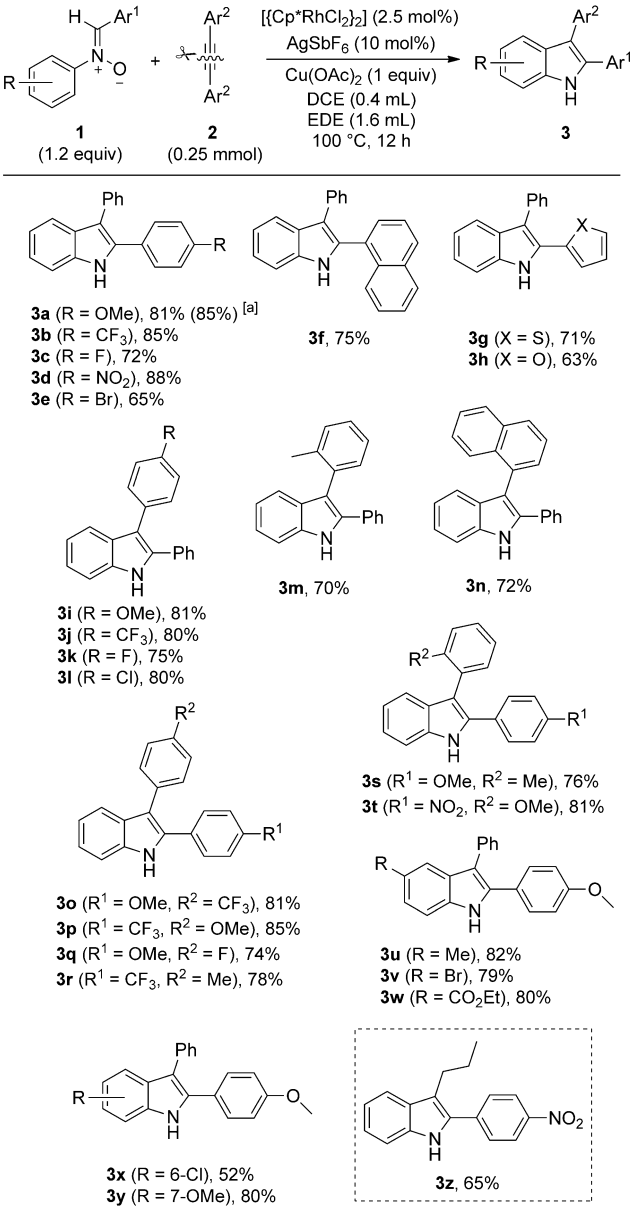


Entry	Change from the standard conditions	**3a**/**4a**[b]	Yield of **3a** [%][b]
1	none	10:1	43
2	120 °C	8:1	31
3	80 °C	3.4:1	30
4	60 °C	5:1	31
5	1 equivalent of $Cu(OAc)_2$	6.5:1	45
6	20 mol% of $Cu(OAc)_2$	1:1	30
7[c]	DCE/THF (1:1)	>25:1	53
8[c]	DCE/1,4-dioxane (1:1)	>25:1	42
9[c]	DCE/DME (1:1)	>25:1	67
10[c]	DCE/EDE (1:1)	>25:1	76
11[c]	DCE/EDE (1:4)	>25:1	85 (81)[d]

[a] Standard reaction conditions: **2a** (0.25 mmol), **1a** (0.3 mmol, 1.2 equiv), $[\{Cp^*RhCl_2\}_2]$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (2 equiv), DCE (2 mL), sealed tube, 100 °C, 12 h. [b] The yield was determined by GC analysis with naphthalene as an internal standard. [c] The reaction was carried out with 1 equivalent of $Cu(OAc)_2$; solvents were combined in the v/v ratio indicated. [d] The yield of the isolated product is given in parentheses. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, EDE = 1,2-diethoxyethane.

by X-ray crystal diffraction of its *N*-tosyl derivative (see the Supporting Information). However, the result was not improved by either increasing or lowering the reaction temperature (Table 1, entries 2–4). Intriguingly, when 1 equivalent of $Cu(OAc)_2$ was used, the yield of **3a** was improved to 45% (Table 1, entry 5). A further decrease in the amount of $Cu(OAc)_2$ to 20 mol% afforded the two products in 60% combined yield (Table 1, entry 6). Unfortunately, the amount of by-product **4a** was also drastically increased. As a mixed solvent proved to be crucial to reactivity in nitrone-assisted C–H activation,[13] we set out to evaluate the solvent effect. To our delight, a 1:1 mixture of DCE and an ether solvent efficiently promoted this reaction and almost completely inhibited the formation of **4a** (Table 1, entries 7–10). During further investigation of the components of the mixed solvent, a 1:4 mixture of DCE and EDE gave the best result (Table 1, entry 11).

The scope of the reaction with respect to both the nitrone and the diaryl alkyne substrate was then explored under the optimized reaction conditions (Scheme 2). Variation of the *C*-aryl ring (Ar^1) of the nitrone was first examined. Substrates with different substituents on the Ar^1 ring were converted into the corresponding unsymmetrically 2,3-diaryl substituted indoles **3a–f** in good yields, regardless of the electronic and steric effects of the substituents. Nitrones bearing 2-furyl and 2-thienyl groups were transformed into the desired products **3g** and **3h** in 71 and 63% yield, respectively. Since only half of the alkyne is regioselectively incorporated into the indole ring, the use of unsymmetrical diaryl alkynes as coupling partners is no longer necessary, thus avoiding the generation of undesired regioisomers. Pleasingly, a variety of symmetrical diaryl alkynes containing electron-rich or electron-deficient functional groups were well tolerated in this reaction, and the desired products **3i–n** were obtained in good yields. Moreover, different combinations of electron-withdrawing and electron-donating groups on the Ar^1 and Ar^2 substituents also afforded the products (compounds **3o–3t**) in good yields. In previous studies,[7d,q,r] reactions of unsymmetrical diaryl alkynes with similar steric and electronic characteristics commonly failed to provide pure regioisomers. In contrast, our method enabled the regioselective preparation of structurally similar unsymmetrically 2,3-diaryl substituted indoles, for example, indoles **3a** and **3i**, **3b** and **3j**, **3c** and **3k**, **3f** and **3n**, and **3o** and **3p**. Indoles bearing substituents at the 5-, 6-, and 7-positions were also synthesized



Scheme 2. Synthesis of unsymmetrically 2,3-diaryl substituted indoles. Reactions were carried out on a 0.25 mmol scale. Yields of the isolated products are given. [a] The yield in parentheses is for a reaction on a 2.5 mmol scale.

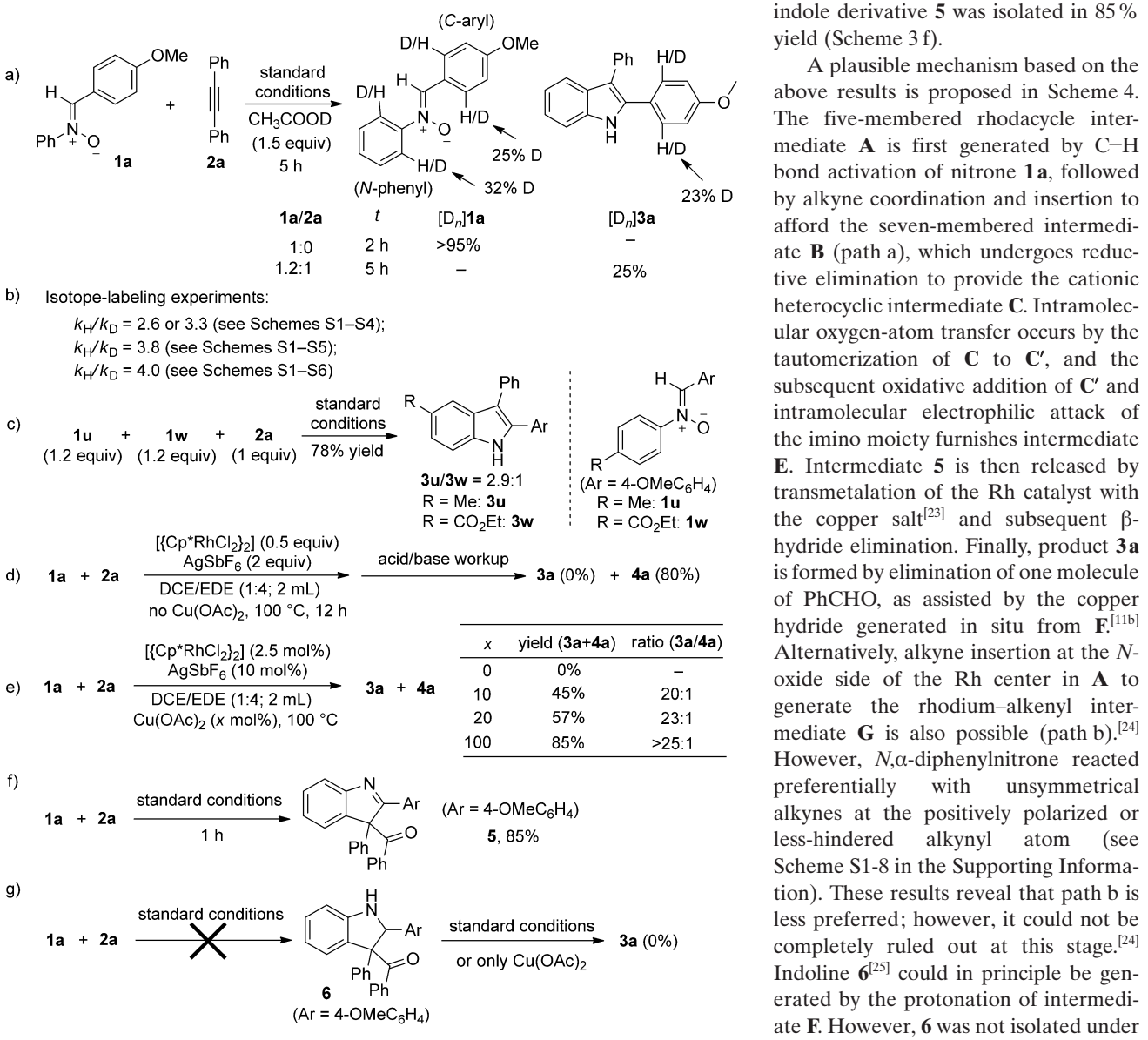
© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

in good yields (products **3u**–**y**), although a slightly lower yield was observed in one case (product **3x**). Significantly, the 2-aryl-3-alkyl indole **3z** was synthesized from the corresponding dialkyl alkyne in 65% yield.[17]

We conducted a series of experiments to probe the reaction mechanism (Scheme 3). When nitrone **1a** was subjected to the standard conditions in the presence of CH_3COOD but without reaction partner **2a**, significant deuterium scrambling was observed (Scheme 3a). However, no H/D exchange was observed on the indole ring when the same reaction was performed in the presence of **2a**; instead 23% deuteration was observed at the positions *meta* to the methoxy group. These results indicated an irreversible C–H insertion step[18] on the indole ring under the reaction conditions. Notable kinetic isotope effects ($k_H/k_D = 2.6$–4.0) were observed in the isotope-labeling experiments (Scheme 3b), thus suggesting that the C–H activation is probably involved in the rate-determining step.[19] Additionally, the treatment of an equimolar amount of nitrones **1u** (4-Me) and **1w** (4-CO_2Et) with alkyne **2a** (0.83 equiv) afforded the corresponding products **3u** and **3w** in a 2.9:1 molar ratio (Scheme 3c). The preferential formation of product **3u** with an electron-rich substituent demonstrates that the C–H activation step might follow the electrophilic aromatic substitution pathway.[20]

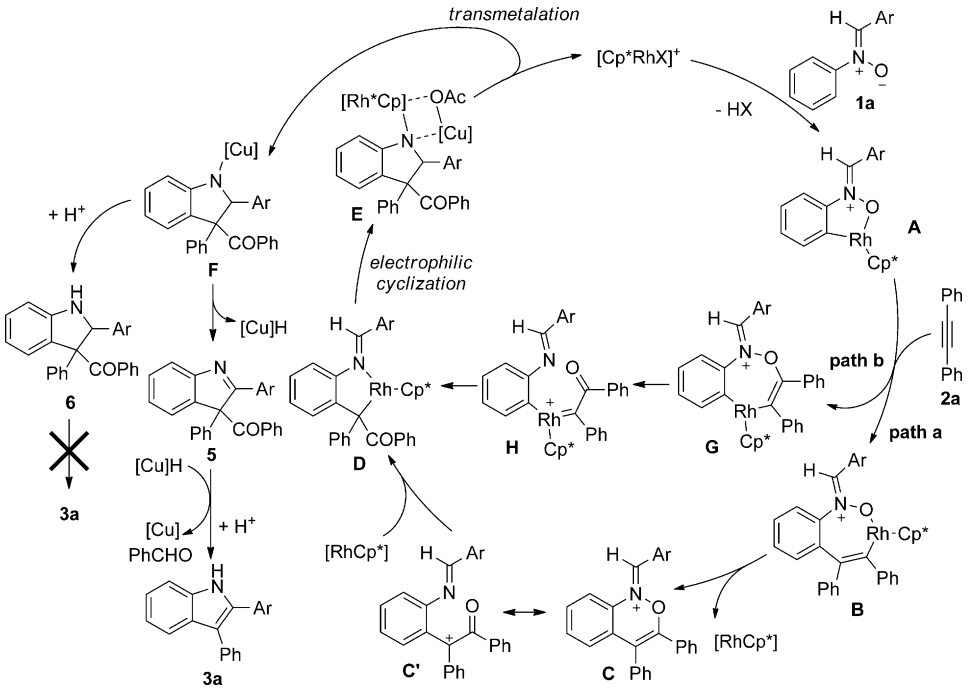
To further understand the reaction process, we performed a control experiment with a stoichiometric amount of the Rh catalyst in the absence of $Cu(OAc)_2$ (Scheme 3d). Interestingly, by-product **4a** was formed in 80% yield, and no **3a** was detected.[21] Furthermore, a catalytic amount of $Cu(OAc)_2$ was sufficient to promote the reaction in moderate yield with excellent selectivity (Scheme 3e). These results indicate that the leading role of the Cu salt is probably to control the selectivity and release the Rh catalyst from the product.[22] Furthermore, when the reaction of **1a** with **2a** was stopped after 1 h, the 3*H*-indole derivative **5** was isolated in 85% yield (Scheme 3f).

A plausible mechanism based on the above results is proposed in Scheme 4. The five-membered rhodacycle intermediate **A** is first generated by C–H bond activation of nitrone **1a**, followed by alkyne coordination and insertion to afford the seven-membered intermediate **B** (path a), which undergoes reductive elimination to provide the cationic heterocyclic intermediate **C**. Intramolecular oxygen-atom transfer occurs by the tautomerization of **C** to **C′**, and the subsequent oxidative addition of **C′** and intramolecular electrophilic attack of the imino moiety furnishes intermediate **E**. Intermediate **5** is then released by transmetalation of the Rh catalyst with the copper salt[23] and subsequent β-hydride elimination. Finally, product **3a** is formed by elimination of one molecule of PhCHO, as assisted by the copper hydride generated in situ from **F**.[11b] Alternatively, alkyne insertion at the *N*-oxide side of the Rh center in **A** to generate the rhodium–alkenyl intermediate **G** is also possible (path b).[24] However, *N*,α-diphenylnitrone reacted preferentially with unsymmetrical alkynes at the positively polarized or less-hindered alkynyl atom (see Scheme S1-8 in the Supporting Information). These results reveal that path b is less preferred; however, it could not be completely ruled out at this stage.[24] Indoline **6**[25] could in principle be generated by the protonation of intermediate **F**. However, **6** was not isolated under the standard conditions, and the



Scheme 3. Mechanistic studies.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 4. Proposed mechanism.

attempted transformation of **6** into **3a** failed (Scheme 3g), thus indicating that indoline **6** might not be involved in this reaction.[26]

In summary, we have developed a regioselective synthesis of unsymmetrically 2,3-diaryl substituted N-unprotected indoles through the rhodium(III)-catalyzed annulation of nitrones with symmetrical diaryl alkynes. Direct C–H annulations with unsymmetrical diaryl alkynes generally occur with unpredictable regioselectivity. In our method, one of the two aryl substituents on the indole ring is derived from the *C*-aryl ring of the nitrone and the other from the alkyne moiety, thus providing the indole products with exclusive regioselectivity. We expect our findings to provide new opportunities in indole chemistry and to find application in the synthesis of complex structures.

Keywords: alkynes · C–H activation · indoles · nitrones · rhodium

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 10613–10617
Angew. Chem. **2015**, *127*, 10759–10763

[1] a) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**; b) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed., Wiley-VCH, Weinheim, **2003**; c) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278; d) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761; e) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73; f) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489.

[2] For reviews on indole synthesis, see: a) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215; e) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195; f) M. Shiri, *Chem. Rev.* **2012**, *112*, 3508; g) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29; h) T. Guo, F. Huang, L. Yu, Z. Yu, *Tetrahedron Lett.* **2015**, *56*, 296.

[3] For selected examples of Fischer indole synthesis, see: a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559; c) S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534; d) D. McAusland, S. Seo, D. G. Pintori, J. Finlayson, M. F. Greaney, *Org. Lett.* **2011**, *13*, 3667; e) S. Gore, S. Baskaran, B. König, *Org. Lett.* **2012**, *14*, 4568; f) A. Porcheddu, M. G. Mura, L. De Luca, M. Pizzetti, M. Taddei, *Org. Lett.* **2012**, *14*, 6112; g) D. Zhao, Z. Shi, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 12426; *Angew. Chem.* **2013**, *125*, 12652.

[4] For selected examples of Larock indole synthesis, see: a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689; b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652.

[5] For selected examples of Buchwald indole synthesis, see: a) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621; b) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 10251; c) J. L. Rutherford, M. P. Rainka, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 15168; d) A. DeAngelis, D. H. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 3434; *Angew. Chem.* **2013**, *125*, 3518.

[6] For indole synthesis through CDC reactions, see: a) Z. Shi, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 9220; *Angew. Chem.* **2012**, *124*, 9354; b) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; *Angew. Chem.* **2008**, *120*, 7340; c) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem. Int. Ed.* **2009**, *48*, 8078; *Angew. Chem.* **2009**, *121*, 8222; d) W. Yu, Y. Du, K. Zhao, *Org. Lett.* **2009**, *11*, 2417; e) Z. H. Guan, Z. Y. Yan, Z. H. Ren, X. Y. Liu, Y. M. Liang, *Chem. Commun.* **2010**, *46*, 2823; f) Z. He, W. Liu, Z. Li, *Chem. Asian J.* **2011**, *6*, 1340; g) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098; h) X. L. Lian, Z. H. Ren, Y. Y. Wang, Z. H. Guan, *Org. Lett.* **2014**, *16*, 3360; i) F. Huang, P. Wu, L. Wang, J. Chen, C. Sun, Z. Yu, *J. Org. Chem.* **2014**, *79*, 10553; j) J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz, F. Glorius, *Chem. Eur. J.* **2011**, *17*, 7298.

[7] For indole synthesis through directing-group-assisted C–H annulation reactions, see: a) M. Shen, G. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina, C. H. Senanayake, *Org. Lett.* **2004**, *6*, 4129; b) D. R. Stuart, M. Bertrand-Laperle, K. M. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474; c) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; *Angew. Chem.* **2009**, *121*, 4642; d) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; e) J. Chen, G. Song, C. L. Pan, X. Li, *Org. Lett.* **2010**, *12*, 5426; f) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem. Int. Ed.* **2011**, *50*, 1338; *Angew. Chem.* **2011**, *123*, 1374; g) J. Chen, Q. Pang, Y. Sun, X. Li, *J. Org. Chem.* **2011**, *76*, 3523; h) H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 19592; i) L. Ackermann,

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

A. V. Lygin, *Org. Lett.* **2012**, *14*, 764; j) B. Liu, C. Song, C. Sun, S. Zhou, J. Zhu, *J. Am. Chem. Soc.* **2013**, *135*, 16625; k) C. Wang, Y. Huang, *Org. Lett.* **2013**, *15*, 5294; l) C. Wang, H. Sun, Y. Fang, Y. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 5795; *Angew. Chem.* **2013**, *125*, 5907; m) W. Song, L. Ackermann, *Chem. Commun.* **2013**, *49*, 6638; n) S. Cai, K. Yang, D. Z. Wang, *Org. Lett.* **2014**, *16*, 2606; o) L. Zheng, R. Hua, *Chem. Eur. J.* **2014**, *20*, 2352; p) W. J. Chen, Z. Lin, *Organometallics* **2015**, *34*, 309; q) G. Zhang, H. Yu, G. Qin, H. Huang, *Chem. Commun.* **2014**, *50*, 4331; r) Y. Hoshino, Y. Shibata, K. Tanaka, *Adv. Synth. Catal.* **2014**, *356*, 1577; s) Z. Fan, S. Song, W. Li, K. Geng, Y. Xu, Z. H. Miao, A. Zhang, *Org. Lett.* **2015**, *17*, 310.

[8] For indole synthesis involving *o*-alkynyl anilines or related compounds, see: a) M. Nakamura, L. Ilies, S. Otsubo, E. Nakamura, *Org. Lett.* **2006**, *8*, 2803; b) B. Z. Lu, W. Zhao, H. X. Wei, M. Dufour, V. Farina, C. H. Senanayake, *Org. Lett.* **2006**, *8*, 3271; c) Z. Shen, X. Lu, *Tetrahedron* **2006**, *62*, 10896; d) S. Cacchi, G. Fabrizi, A. Goggiamani, *Adv. Synth. Catal.* **2006**, *348*, 1301; e) N. Isono, M. Lautens, *Org. Lett.* **2009**, *11*, 1329; f) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Perboni, A. Sferrazza, P. Stabile, *Org. Lett.* **2010**, *12*, 3279; g) T. Shibata, H. Hirashima, M. Kasagawa, K. Tsuchikama, K. Endo, *Synlett* **2011**, 2171; h) B. Yao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2012**, *51*, 12311; *Angew. Chem.* **2012**, *124*, 12477; i) B. Z. Lu, H. W. Wei, Y. Zhang, W. Zhao, M. Dufour, G. Li, V. Farina, C. H. Senanayake, *J. Org. Chem.* **2013**, *78*, 4558; j) S. P. Breazzano, Y. B. Poudel, D. L. Boger, *J. Am. Chem. Soc.* **2013**, *135*, 1600; k) D. Shan, Y. Gao, Y. Jia, *Angew. Chem. Int. Ed.* **2013**, *52*, 4902; *Angew. Chem.* **2013**, *125*, 5002; l) P. Tao, Y. Jia, *Chem. Commun.* **2014**, *50*, 7367; m) X. Zhang, Y. Li, H. Shi, L. Zhang, S. Zhang, X. Xu, Q. Liu, *Chem. Commun.* **2014**, *50*, 7306; n) B. Zhou, Y. Yang, H. Tang, J. Du, H. Feng, Y. Li, *Org. Lett.* **2014**, *16*, 3900.

[9] For indole synthesis involving azides, see: a) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012; b) K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem. Int. Ed.* **2011**, *50*, 1702; *Angew. Chem.* **2011**, *123*, 1740; c) B. J. Stokes, S. Liu, T. G. Driver, *J. Am. Chem. Soc.* **2011**, *133*, 4702; d) Q. Nguyen, T. Nguyen, T. G. Driver, *J. Am. Chem. Soc.* **2013**, *135*, 620; e) Y. Goriya, C. V. Ramana, *Chem. Commun.* **2014**, *50*, 7790.

[10] For other examples, see: a) T. Fukuyama, X. Chen, G. Peng, *J. Am. Chem. Soc.* **1994**, *116*, 3127; b) H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi, T. Fukuyama, *J. Am. Chem. Soc.* **1999**, *121*, 3791; c) C. Mukai, Y. Takahashi, *Org. Lett.* **2005**, *7*, 5793; d) G. Babu, A. Orita, J. Otera, *Org. Lett.* **2005**, *7*, 4641; e) K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes, Y. Cai, *Org. Lett.* **2006**, *8*, 5769; f) S. Tanimori, H. Ura, M. Kirihata, *Eur. J. Org. Chem.* **2007**, 3977; g) A. Saito, A. Kanno, Y. Hanzawa, *Angew. Chem. Int. Ed.* **2007**, *46*, 3931; *Angew. Chem.* **2007**, *119*, 4005; h) M. Tursky, L. L. R. Lorentz-Petersen, L. B. Olsen, R. Madsen, *Org. Biomol. Chem.* **2010**, *8*, 5576; i) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; j) S. Jana, M. D. Clements, B. K. Sharp, N. Zheng, *Org. Lett.* **2010**, *12*, 3736; k) D. Janreddy, V. Kavala, J. W. J. Bosco, C. W. Kuo, C. F. Yao, *Eur. J. Org. Chem.* **2011**, 2360; l) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270; m) B. V. S. Reddy, M. R. Reddy, Y. G. Rao, J. S. Yadav, B. Sridhar, *Org. Lett.* **2013**, *15*, 464; n) S. Zhu, A. Das, L. Bui, H. Zhou, D. P. Curran, M. Rueping, *J. Am. Chem. Soc.* **2013**, *135*, 1823; o) Y. Liang, K. Yu, B. Li, S. Xu, H. Song, B. Wang, *Chem. Commun.* **2014**, *50*, 6130; p) M. K. Manna, A. Hossian, R. Jana, *Org. Lett.* **2015**, *17*, 672.

[11] a) G. A. Kraus, H. Guo, *J. Org. Chem.* **2009**, *74*, 5337; b) T. Kim, K. Kim, *Tetrahedron Lett.* **2010**, *51*, 868; c) X. Dou, W. Yao, S. Wen, Y. Lu, *Chem. Commun.* **2014**, *50*, 9469.

[12] For selected reviews, see: a) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; b) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; e) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281; f) X. S. Zhang, K. Chen, Z. J. Shi, *Chem. Sci.* **2014**, *5*, 2146; g) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.* **2015**, *44*, 1155; h) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007.

[13] C. Wang, D. Wang, H. Yan, H. Wang, B. Pan, X. Xin, X. Li, F. Wu, B. Wan, *Angew. Chem. Int. Ed.* **2014**, *53*, 11940; *Angew. Chem.* **2014**, *126*, 12134.

[14] N. Duguet, A. M. Z. Slawin, A. D. Smith, *Org. Lett.* **2009**, *11*, 3858.

[15] For reports on carbon–carbon triple-bond cleavage, see: a) H. Liu, M. Feng, X. Jiang, *Chem. Asian J.* **2014**, *9*, 3360; b) T. Shen, T. Wang, C. Qin, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 6677; *Angew. Chem.* **2013**, *125*, 6809; c) N. Okamoto, M. Ishikura, R. Yanada, *Org. Lett.* **2013**, *15*, 2571; d) Q. Liu, P. Chen, G. Liu, *ACS Catal.* **2013**, *3*, 178; e) H. Z. Xie, Q. Gao, Y. Liang, H. S. Wang, Y. M. Pan, *Green Chem.* **2014**, *16*, 2132; f) J. Sun, F. Wang, H. Hu, X. Wang, H. Wu, Y. Liu, *J. Org. Chem.* **2014**, *79*, 3992; g) T. Shimada, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6646; h) D. Y. Lee, B. S. Hong, E. G. Cho, H. Lee, C. H. Jun, *J. Am. Chem. Soc.* **2003**, *125*, 6372; i) S. Datta, C. L. Chang, K. L. Yeh, R. S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 9294; j) Y. Liu, F. Song, S. Guo, *J. Am. Chem. Soc.* **2006**, *128*, 11332; k) A. Wang, H. Jiang, *J. Am. Chem. Soc.* **2008**, *130*, 5030; l) M. Gaydou, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 13468; *Angew. Chem.* **2013**, *125*, 13710.

[16] Only a handful of examples of the synthesis of N-unprotected indoles by intermolecular C–H annulation with alkynes have been reported; see Refs. [3g, 7l,o,q].

[17] Unfortunately, because of the instability of *C*-alkyl nitrones, we have not yet succeeded in using this protocol to synthesize 2-alkyl-3-aryl or 2-alkyl-3-alkyl-substituted indoles.

[18] T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565.

[19] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066; *Angew. Chem.* **2012**, *124*, 3120.

[20] The high KIE values (2.6 – 4.0) observed in this reaction suggest that slow hydrogen abstraction might occur after the electrophilic attack of Rh on the *N*-phenyl ring in the C–H activation process. For similar observations, see Ref. [13]; see also: X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837.

[21] With 0.25 equivalents of $[\{Cp^*RhCl_2\}_2]$ (50 mol% Rh), **4a** was isolated in 35% yield, and no **3a** was detected.

[22] The use of $Fe(OAc)_2$ or $Mn(OAc)_2$ (1 equiv) instead of $Cu(OAc)_2$ did not afford any product. The replacement of $Cu(OAc)_2$ with $Cu(OTf)_2$ (1 equiv) only gave **3a** in 30% yield.

[23] F. W. Patureau, T. Besset, N. Kuhl, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2154.

[24] X. Zhang, Z. Qi, X. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 10794; *Angew. Chem.* **2014**, *126*, 10970.

[25] During the preparation of this manuscript, the rhodium(III)-catalyzed cyclization of aryl nitrones with diaryl alkynes was reported to afford indolines in the absence of copper salts: R. B. Dateer, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4908.

[26] For the formation of by-product **4a**, see the Supporting Information.

Received: May 1, 2015
Published online: July 14, 2015

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim