DOI: 10.1002/adsc.200900004

# Copper-Catalyzed *N*-Arylation/Hydroamin(d)ation Domino Synthesis of Indoles and its Application to the Preparation of a Chek1/KDR Kinase Inhibitor Pharmacophore

Lutz Ackermann,[a,*] Sebastian Barfüßer,[a] and Harish K. Potukuchi[a]

[a] 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

Received: January 4, 2009; Published online: April 30, 2009

Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday.

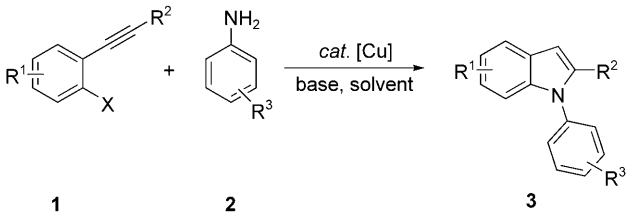
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900004.

**Abstract:** Inexpensive copper catalysts allow for efficient syntheses of *N*-aryl-, *N*-acyl-, or *N*-H-(aza)indoles starting from *ortho*-alkynylbromoarenes. The broad scope of this domino *N*-arylation/hydroamin(d)ation process is highlighted by the synthesis of highly functionalized indoles, as well as of a Chek1/KDR inhibitor pharmacophore.

**Keywords:** amination; arylation; catalysis; copper; hydroamination; indoles

## Introduction

Indoles are the most abundant heterocycles in biologically active compounds and natural products.[1,2] As a consequence, a continued strong demand exists for the development of generally applicable syntheses of this structural motif. Recently developed metal-catalyzed processes[3–5] proved complementary to conventional indole syntheses,[6–8] and allowed for reactions to be performed under remarkably mild reaction conditions.[9–13] Particularly, protocols relying on addition reactions of nitrogen nucleophiles onto alkynes[5,14–19] set the stage for the development of synthetically useful approaches to diversely-substituted indoles.[11,20,21] Thus, intramolecular hydroamination reactions employing *ortho*-alkynylanilines enabled efficient syntheses of this heterocyclic backbone.[20,22] We, however, became interested in devising reaction conditions for palladium-catalyzed domino[23–25] reactions, that allowed for the direct transformation of easily accessible *ortho*-alkynylhaloarenes[13m] and *ortho*-dihaloarenes to the corresponding indole derivatives.[26–28] Given the recent renewed interest in Ullman–Goldberg *N*-arylations,[29–31] partly due to the generally lower costs associated with the use of copper catalysts,[32] we probed *in-situ* generated copper complexes for modular indole syntheses employing *ortho*-alkynylhaloarenes **1** as substrates (Scheme 1).[26,33] Thus, we




1 2 3

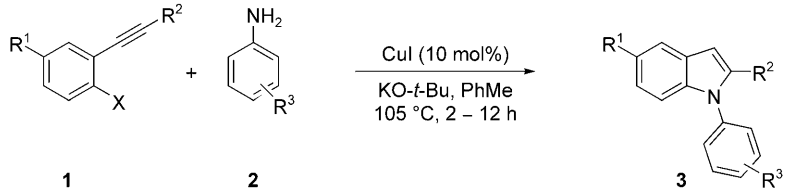
**Scheme 1.** Copper-catalyzed domino synthesis of substituted indoles **3**.

reported selected examples of a domino synthesis of *N*-arylindoles **3** with a catalytic system relying on inexpensive CuI.[26] Herein, we wish to provide a full account on these studies, including the development of reaction conditions for the preparation of *N*-acyl-, and *N*-H-(aza)indoles, as well as an application to the synthesis of a Chek1/KDR kinase inhibitor pharmacophore.

## Results and Discussion

"Nitrogen ligand-free" copper-catalyzed amination reactions were previously shown to proceed efficiently, provided that KO-*t*-Bu was employed as base.[34] Consequently, we explored the possibility of accomplishing a copper-catalyzed domino indole synthesis with inexpensive CuI as catalyst (Table 1). Preliminary

**Table 1.** Copper-catalyzed synthesis of *N*-arylindoles **3**.[a]




**1** **2** **3**

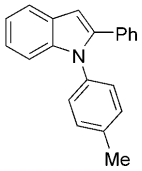
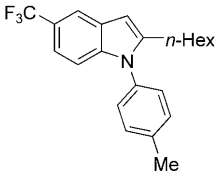
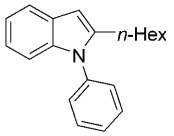
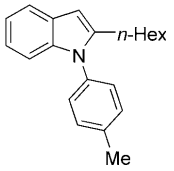
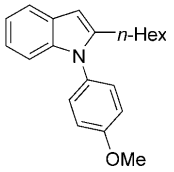
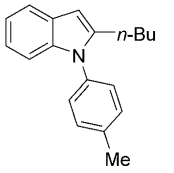
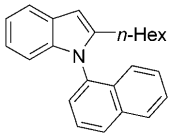
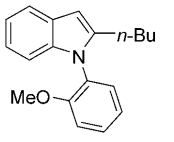
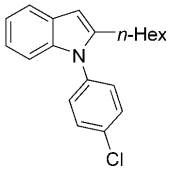
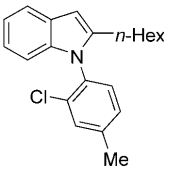
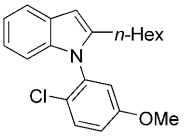
| Entry | X | $R^1$ | $R^2$ | | $R^3$ | Product | | Isolated Yield |
|---|---|---|---|---|---|---|---|---|
| 1 | Cl | H | Ph | **1a** | 4-Me |  | **3a** | 21% |
| 2 | Cl | $CF_3$ | *n*-Hex | **1b** | 4-Me |  | **3b** | 53%[b] |
| 3 | Br | H | *n*-Hex | **1c** | H |  | **3c** | 84% |
| 4 | Br | H | *n*-Hex | **1c** | 4-Me |  | **3d** | 67% |
| 5 | Br | H | *n*-Hex | **1c** | 4-OMe |  | **3e** | 60% |
| 6 | Br | H | *n*-Bu | **1d** | 4-Me |  | **3f** | 75% |
| 7 | Br | H | *n*-Hex | **1c** | 1-naphthyl |  | **3g** | 77% |
| 8 | Br | H | *n*-Bu | **1d** | 2-OMe |  | **3h** | 69% |
| 9 | Br | H | *n*-Hex | **1c** | 4-Cl |  | **3i** | 70% |

**Table 1.** (Continued)

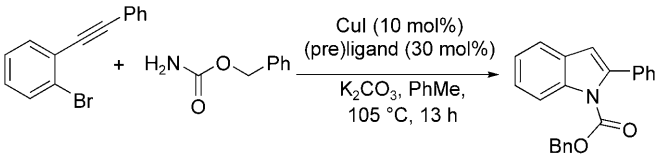
| Entry | X | $R^1$ | $R^2$ | | $R^3$ | Product | | Isolated Yield |
|---|---|---|---|---|---|---|---|---|
| 10 | Br | H | *n*-Hex | **1c** | 2-Cl-4-Me |  | **3j** | 72% |
| 11 | Br | H | *n*-Hex | **1c** | 2-Cl-5-OMe |  | **3k** | 60% |

[a] *Reaction conditions:* **1** (1.0 mmol), **2** (1.2 mmol), CuI (10 mol%), KO-*t*-Bu (3.0 mmol), PhMe (3–5 mL), 105 °C, 2–12 h.
[b] GC conversion.

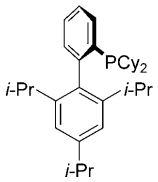
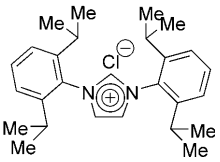
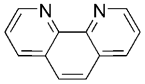
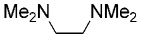
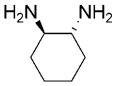
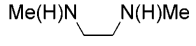
studies revealed that KO-*t*-Bu was superior among a variety of bases (e.g., NaO-*t*-Bu, or LiO-*t*-Bu). Contrary to palladium-catalyzed transformations,[26,27] the use of chlorides as leaving groups in substrates **1a** and **1b**, unfortunately, only gave rise to unsatisfactory results (entries 1, and 2). However, synthetically useful isolated yields were accomplished with *ortho*-alkynylbromoarenes (entries 3–11). Notably, *ortho*-substituents on more sterically hindered aniline derivatives were well tolerated (entries 7, and 8), as were chlorides as functionalities, which resulted in the chemoselective preparation of substituted indoles **3i–3k** (entries 9–11). As to the mechanism of this "nitrogen ligand-free" copper-catalyzed transformation, experiments with a secondary amine suggest a reaction sequence consisting of intermolecular hydroamination, followed by intramolecular *N*-arylation.

A significant advantage of using inexpensive copper complexes for catalytic C–N bond formations, particularly when compared with the corresponding palladium-catalyzed processes,[35] is represented by the efficacy, with which less nucleophilic amides **4** can be arylated.[29–31] Therefore, we became interested in optimizing reaction conditions for the copper-catalyzed synthesis of *N*-acylindole[33] **5a** (Table 2). Preliminary experiments revealed that toluene, among a variety of solvents (NMP, DMSO, DMPU, DMF, and THF), proved to give rise to optimal results. Furthermore, the use of $K_2CO_3$ as base was found superior, even when being compared with reactions performed with $Cs_2CO_3$ as base. Subsequently, we probed representative (pre)ligands for the envisioned copper-catalyzed *N*-arylation/hydroamidation domino reaction. While biarylphosphine **6**,[36] carbene-precursor **7**,[37,38] and L-proline (**8**),[29,39] provided unsatisfactory results (entries 2–4), more promising catalysis could be achieved with N,N-bidentate ligands (entries 5–8), with vicinal diamine **12**[33] giving rise to high conversions to the desired product **5a** (entry 8). Here, a

**Table 2.** Evaluation of (pre)ligands for the copper-catalyzed synthesis of indole **5a**.[a]




**1e** **4a** **5a**

| Entry | Ligand | | Yield |
|---|---|---|---|
| 1 | – | | – |
| 2 |  | **6** | <5% |
| 3 |  | **7** | <5% |
| 4 | L-proline | **8** | <5% |
| 5 |  | **9** | <5% |
| 6 |  | **10** | <5% |
| 7 |  | **11** | 20% |
| 8 | | | 75% |
| 9 |  | **12** | 30%[b] |
| 10 | | | <5%[c] |

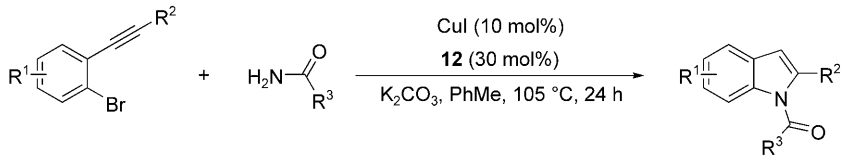
[a] *Reaction conditions:* **1e** (1.0 equiv.), **4a** (1.2 equiv.), CuI (10 mol%), (pre)ligand (30 mol%), $K_2CO_3$ (2.0 equiv.), PhMe (4 mL), 105 °C; GC conversion.
[b] CuI (10 mol%), **12** (20 mol%).
[c] CuI (1 mol%), **12** (3 mol%).

ligand to copper ratio of 3/1 was found beneficial (entries 8–10).

With a highly active catalytic system in hand, we explored its scope in the preparation of various *N*-acylindoles (Table 3). In addition to benzyl carbamate (entries 1–4), *tert*-butyl carbamate turned out to be a suitable nucleophile (entries 5–11). Also amides could be employed in the domino synthesis, thus, enabling

**Table 3.** Scope of copper-catalyzed synthesis of *N*-acylindoles **5**.[a]




**1** **4** **5**

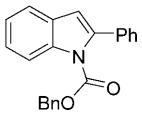
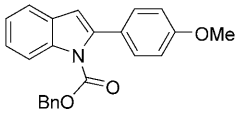
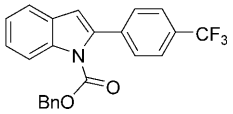
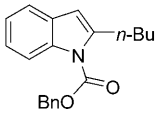
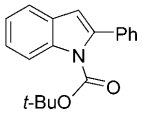
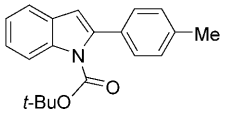
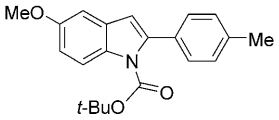
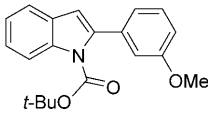
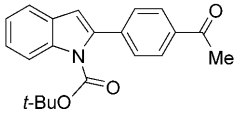
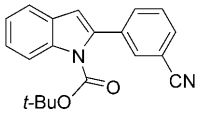
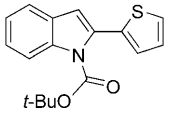
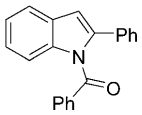
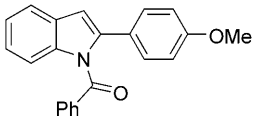
| Entry | $R^1$ | $R^2$ | | $R^3$ | Product | | Isolated Yield |
|---|---|---|---|---|---|---|---|
| 1 | H | Ph | **1e** | BnO |  | **5a** | 57% |
| 2 | H | 4-$MeOC_6H_4$ | **1f** | BnO |  | **5b** | 56% |
| 3 | H | 4-$F_3CC_6H_4$ | **1g** | BnO |  | **5c** | 55% |
| 4 | H | *n*-Bu | **1d** | BnO |  | **5d** | 52% |
| 5 | H | Ph | **1e** | *t*-BuO |  | **5e** | 73% |
| 6 | H | 4-$MeC_6H_4$ | **1h** | *t*-BuO |  | **5f** | 63% |
| 7 | MeO | 4-$MeC_6H_4$ | **1i** | *t*-BuO |  | **5g** | 58% |
| 8 | H | 3-$MeOC_6H_4$ | **1j** | *t*-BuO |  | **5h** | 65% |
| 9 | H | 4-$MeC(O)C_6H_4$ | **1k** | *t*-BuO |  | **5i** | 65% |
| 10 | H | 3-$NCC_6H_4$ | **1l** | *t*-BuO |  | **5j** | 63% |
| 11 | H | 2-thienyl | **1m** | *t*-BuO |  | **5k** | 61% |

**Table 3.** (Continued)

| Entry | $R^1$ | $R^2$ | | $R^3$ | Product | | Isolated Yield |
|---|---|---|---|---|---|---|---|
| 12 | H | Ph | **1e** | Ph |  | **5l** | 62% |
| 13 | H | 4-$MeOC_6H_4$ | **1f** | Ph |  | **5m** | 71% |

[a] *Reaction conditions:* **1** (1.0 equiv.), **4** (1.2 equiv.), CuI (10 mol%), **12** (30 mol%), $K_2CO_3$ (2.0 equiv.), PhMe (4 mL), 105 °C.

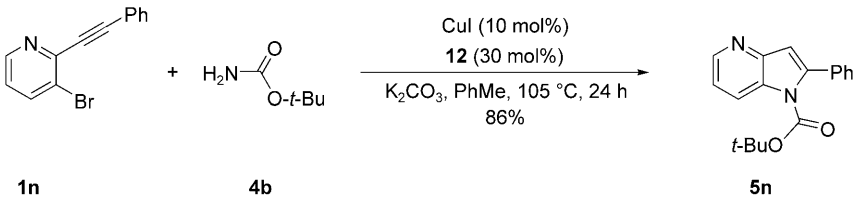
the preparation of *N*-acylindoles **5l** and **5m** (entries 12, and 13). Notably, the mild reaction conditions allowed for the chemoselective conversion of highly functionalized starting materials, such as *ortho*-alkynylbromoarenes bearing a keto- (entry 9) or a cyano group (entry 10), as well as a thienyl substituent (entry 11).

Furthermore, the optimized protocol was found to be applicable to the synthesis of azaindole **5n** employing pyridyl bromide **1n** as electrophilic starting material (Scheme 2).

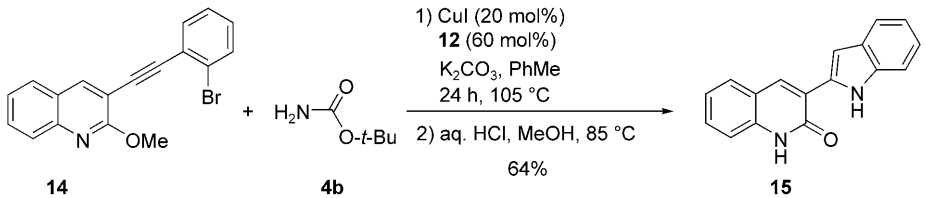
Considering the importance of free *N*-H indoles **13** in biologically active compounds, we subsequently studied their one-pot preparation starting from *ortho*-alkynylbromoarenes **1** (Table 4). The use of carbamate **4b** as nucleophile in the copper-catalyzed domino transformation, along with a subsequent simple treatment with trifluoroacetic acid, set the stage for an efficient access to the desired *N*-H indoles **13**. Thereby, a variety of substituted products **13** was obtained displaying valuable functional groups, such as an ester (entry 7), a nitrile (entry 8), a ketone (entry 9), a chloride (entry 10), or an amide (entry 11).

Mechanistic studies suggest that the use of less nucleophilic carbamates or amides **4** as coupling partners, as well as of diamine **12** as ligand results in a sequence comprising intermolecular amidation,[33] and subsequent intramolecular hydroamination.[22a,b]

Tyrosine kinases are an important family of enzymes which are supposed to be of significance for signal transduction in various cellular functions. As a consequence, these enzymes have been implicated in a variety of diseases or conditions such as, *inter alia*, angiogenesis, cancer, or tumor growth.[40–44] The kinase insert domain receptor (KDR) is a human tyrosine kinase, displaying a high affinity for vascular endothelial growth factor (VEGF), and is, hence, believed to be a primary mediator of tumor-induced angiogenesis.[45,46] Recently, 1*H*-indol-2-yl-1*H*-quinolin-2-ones were identified at Merck as a key pharmacophore of novel effective inhibitors of the KDR receptor, and are, therefore, potentially useful for the prevention and treatment of tumor-induced angiogenesis.[47–51] Furthermore, indol-2-yl-quinolin-2-ones were also shown to be potent Chek1 kinase inhibitors.[52] As a result, various strategies were devised for the synthesis of the indol-2-yl-quinolin-2-ones structural



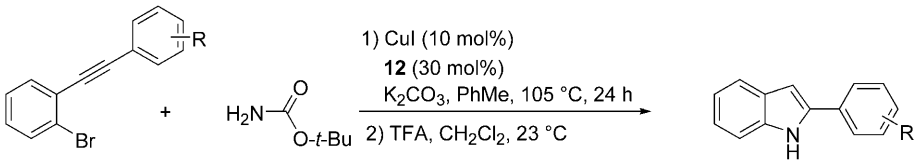

**Scheme 2.** Copper-catalyzed preparation of azaindole **5n**.



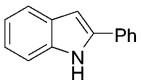
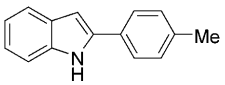
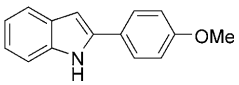
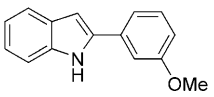
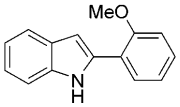
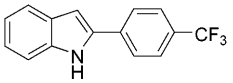
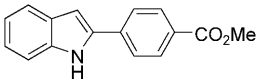
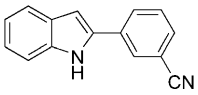
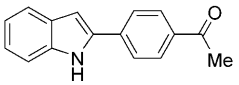
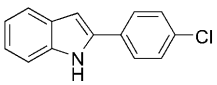
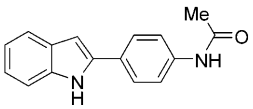

**Scheme 3.** Synthesis of the pharmacophore **15** of Chek1/KDR kinase inhibitors.

**Table 4.** Copper-catalyzed domino synthesis of free *N*-H indole **13**.[a]




**1** **4b** **13**

| Entry | R | | Product | | Isolated Yield |
|---|---|---|---|---|---|
| 1 | H | **1e** |  | **13a** | 69% |
| 2 | 4-Me | **1h** |  | **13b** | 55% |
| 3 | 4-OMe | **1f** |  | **13c** | 65% |
| 4 | 3-OMe | **1j** |  | **13d** | 64% |
| 5 | 2-OMe | **1o** |  | **13e** | 50% |
| 6 | 4-$CF_3$ | **1g** |  | **13f** | 72% |
| 7 | 4-$CO_2Me$ | **1p** |  | **13g** | 68% |
| 8 | 3-CN | **1l** |  | **13h** | 57% |
| 9 | 4-C(O)Me | **1k** |  | **13i** | 54% |
| 10 | 4-Cl | **1q** |  | **13j** | 72% |
| 11 | 4-NHC(O)Me | **1r** |  | **13k** | 55% |

[a] *Reaction conditions:* a) **1** (1.0 equiv.), **4b** (1.2 equiv.), CuI (10 mol%), **12** (30 mol%), $K_2CO_3$ (2.0 equiv.), PhMe (4 mL), 105 °C, 24 h; b) TFA, $CH_2Cl_2$, 23 °C.

motif.[47–55] In order to highlight the scope of our copper-catalyzed domino synthesis, we subjected quinoline **14** to the optimized reaction conditions. We were delighted to observe that indol-2-yl-quinolin-2-ones **15** could be isolated in good yield within a one-pot strategy consisting of the copper-catalyzed domino indole synthesis and subsequent treatment with aqueous HCl (Scheme 3).

## Conclusions

We have presented reaction conditions for copper-catalyzed domino *N*-arylation/hydroamination syntheses of indole derivatives starting from *ortho*-alkynylbromoarenes. While *N*-arylindoles could be obtained with a simple "nitrogen ligand-free" catalytic system, an *in-situ* generated copper complex derived from vicinal diamine **12** enabled the preparation of the corre-

sponding *N*-acyl- and *N*-H-indoles. The broad scope of these methodologies was illustrated with the synthesis of diversely functionalized indoles and azaindoles, as well as with an efficient preparation of the pharmacophore **15** of effective Chek1/KDR kinase inhibitors.

## Experimental Section

### General Remarks

Catalytic reactions were carried out under a $N_2$ atmosphere using pre-dried glassware. *ortho*-Alkynylbromoarenes **1**, and **14** were prepared in analogy to previously described methodologies.[56] Other starting materials were obtained from commercial sources, and were used without further purification. Yields refer to isolated compounds, estimated to be >95% pure as determined by $^1$H NMR and GC. Flash chromatography: Macherey–Nagel silica gel 60 (70–230 mesh). NMR spectra were recorded on Bruker AMX 600, Varian VXR400S, Bruker AM 250, Unity 300 or Inova 500 instruments in the solvent indicated; chemical shifts (δ) are given in ppm.

### Representative Procedure A: Copper-Catalyzed Synthesis of *N*-Arylindole 3d (Table 1, entry 4)

To a solution of CuI (18 mg, 0.10 mmol, 10 mol%) and KO-*t*-Bu (336 mg, 3.0 mmol) in PhMe (3 mL) was added **1c** (265 mg, 1.0 mmol) and 4-methylaniline (129 mg, 1.2 mmol) at ambient temperature. The resulting mixture was stirred at 105 °C for 2 h. $CH_2Cl_2$ (50 mL) and aqueous HCl (2N, 50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with $CH_2Cl_2$ (2×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/$Et_2O$, 200/1→50/1) to afford **3d** as a yellow oil; yield: 195 mg (67%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.60 (m, 1H), 7.35 (d, $J$ = 8.0 Hz, 2H), 7.25 (d, $J$ = 8.0 Hz, 2H), 7.15–7.05 (m, 3H), 6.43 (s, 1H), 2.63 (t, $J$ = 7.6 Hz, 2H), 2.49 (s, 3H), 1.61 (quint., $J$ = 7.5 Hz, 2H), 1.40–1.20 (m, 6H), 0.88 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 142.1, 138.4, 137.6, 135.4, 130.0, 128.0, 128.0, 120.8, 119.8, 119.5, 110.0, 99.8, 31.5, 28.9, 28.6, 27.0, 22.5, 21.2, 14.0; IR (KBr): ν = 3054, 2954, 2926, 2856, 1608, 1514, 1457, 1394, 1211, 1016, 817, 746 cm$^{-1}$; MS (EI): *m/z* (relative intensity) = 291 (38) [M$^+$], 234 (28), 221 (100), 220 (65), 204 (29); HR-MS (EI): *m/z* = 291.1971, calcd. for $C_{21}H_{25}N$: 291.1987.

### Representative Procedure B: Copper-Catalyzed Synthesis of *N*-Acylindole 5e (Table 3, entry 5)

A suspension of CuI (19 mg, 0.10 mmol, 10 mol%), $K_2CO_3$ (0.276 g, 2.00 mmol), **4b** (0.141 g, 1.20 mmol), **12** (0.026 g, 0.30 mmol, 30 mol%) and **1e** (0.257 g, 1.00 mmol) in PhMe (4 mL) was stirred under $N_2$ for 24 h at 105 °C. $H_2O$ (50 mL) and $Et_2O$ (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with $Et_2O$ (2×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/$Et_2O$ 50:1) to afford **5e** as a white solid; yield: 0.215 g (73%); mp 75.8–76.9 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.27–8.26 (m, 1H), 7.59–7.58 (m, 1H), 7.46–7.35 (m, 6H), 7.30–7.27 (m, 1H), 6.59 (d, $J$ = 3.5 Hz, 1H), 1.34–1.33 (m, 9H); $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 150.2, 140.5, 137.4, 135.0, 129.2, 128.7, 127.7, 127.5, 124.3, 122.9, 120.4, 115.2, 109.9, 83.3, 27.5; IR (ATR): ν = 3025, 2981, 1726, 1561, 1452, 1336, 1223, 1133, 1016, 842, 816, 749, 700 cm$^{-1}$; MS (DEI, 70 eV): *m/z* = 293 ([M$^+$] 53), 237 (94), 220 (11), 193 (100), 165 (20), 57 (59); HR-MS (EI): *m/z* = 293.1421, calcd. for $C_{19}H_{19}NO_2$: 293.1416. The spectral data are in accordance with those reported in the literature.[57]

## Acknowledgements

*Support by the DFG, the DAAD (fellowship to HKP), the GIF, and Sanofi-Aventis is gratefully acknowledged.*

## References

[1] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930.
[2] G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911.
[3] L. Ackermann, *Modern Arylation Reactions*, Wiley-VCH, Weinheim, **2009**.
[4] A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn., Wiley-VCH, Weinheim, **2004**.
[5] M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, 2nd edn., Wiley-VCH, Weinheim, **2004**.
[6] T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, 2nd edn., Wiley-VCH, Weinheim, **2003**.
[7] T. L. Gilchrist, *Heterocyclic Chemistry*, 3rd edn., Addison Wesley Longman Limited, Harlow, **1997**.
[8] J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 4th edn., Blackwell Science Ltd, Oxford, **2000**.
[9] L. Ackermann, *Synlett* **2007**, 507–526.
[10] S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920.
[11] K. Krüger, A. Tillack, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2153–2167.
[12] I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198.
[13] For selected recent examples, see: a) K. Alex, A. Tillack, N. Schwarz, M. Beller, *Angew. Chem.* **2008**, *120*, 2337–2340; *Angew. Chem. Int. Ed.* **2008**, *47*, 2304–2307; b) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475; c) Y.-Q. Fang, M. Lautens, *J. Org. Chem.* **2008**, *73*, 538–549; d) C. S. Bryan, M. Lautens, *Org. Lett.* **2008**, *10*, 4633–4636; e) T. Jensen, H. Pedersen, B. Bang-Andersen, R. Madsen, M. Jørgensen, *Angew. Chem.* **2008**, *120*, 902–904; *Angew. Chem. Int. Ed.* **2008**, *47*, 888–890; f) H. Ohno, Y. Ohta, S. Oishi, N. Fujii, *Angew. Chem.* **2007**, *119*, 2345–2348; *Angew. Chem. Int. Ed.* **2007**, *46*, 2295–2298; g) B. M. Trost, A.

McClory, *Angew. Chem.* **2007**, *119*, 2120–2123; *Angew. Chem. Int. Ed.* **2007**, *46*, 2074–2077; h) M. McLaughlin, M. Palucki, I. W. Davies, *Org. Lett.* **2006**, *8*, 3307–3310; i) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025; j) A. L. Odom, *Dalton Trans.* **2005**, 225–233; k) M. C. Willis, G. N. Brace, I. P. Holmes, *Angew. Chem.* **2005**, *117*, 407–410; *Angew. Chem. Int. Ed.* **2005**, *44*, 403–406; l) T. Shimada, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 10546–10547; m) H. Siebeneicher, I. Bytschkov, S. Doye, *Angew. Chem.* **2003**, *115*, 3151–3153; *Angew. Chem. Int. Ed.* **2003**, *42*, 3042–3044; n) M. A. Campo, Y. Huang, T. Yao, Q. Tian, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 11506–11507, and references cited therein.

[14] T. E. Mueller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795–3892.

[15] R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391.

[16] K. C. Hultzsch, *Adv. Synth. Catal.* **2005**, *347*, 367–391.

[17] M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448–3479; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398.

[18] F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159.

[19] For representative examples of hydroamination reactions from our laboratories, see: a) L. Ackermann, A. Althammer, *Synlett* **2008**, 995–998; b) L. Ackermann, L. T. Kaspar, *J. Org. Chem.* **2007**, *72*, 6149–6153; c) L. Ackermann, L. T. Kaspar, A. Althammer, *Org. Biomol. Chem.* **2007**, *5*, 1975–1978; d) L. Ackermann, *Organometallics* **2003**, *22*, 4367–4368.

[20] G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309.

[21] Selected hydroamination-based indole syntheses from our laboratories: a) L. Ackermann, R. Sandmann, A. Villar, L. T. Kaspar, *Tetrahedron* **2008**, *64*, 769–777; b) L. Ackermann, A. Althammer, *Synlett* **2006**, 3125–3129; c) L. Ackermann, L. T. Kaspar, C. J. Gschrei, *Chem. Commun.* **2004**, 2824–2825; d) L. Ackermann, R. Born, *Tetrahedron Lett.* **2004**, *45*, 9541–9544.

[22] For early examples of copper-mediated reactions, see: a) C. E. Castro, R. D. Stephens, *J. Org. Chem.* **1963**, *28*, 2163; b) C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem.* **1966**, *31*, 4071–4078; for early examples of catalytic transformations, see: c) K. Utimoto, H. Miwa, H. Nozaki, *Tetrahedron Lett.* **1981**, *22*, 4277–4278; d) K. Irtani, S. Matsubara, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 1799–1802; e) A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1989**, *30*, 2581–2584; f) S. Cacchi, V. Carnicelli, F. Marinelli, *J. Organomet. Chem.* **1994**, *475*, 289–296.

[23] For selected reviews on palladium-catalyzed domino or cascade coupling reactions, see, for example: a) P. von Zezschwitz, A. de Meijere, *Top. Organomet. Chem.* **2006**, *19*, 49–89; b) A. de Meijere, P. von Zezschwitz, S. Braese, *Acc. Chem. Res.* **2005**, *38*, 413–422; c) A. de Meijere, P. von Zezschwitz, H. Nuske, B. Stulgies, *J. Organomet. Chem.* **2002**, *653*, 129–140.

[24] L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[25] A recent example from our laboratories: L. Ackermann, A. Althammer, *Angew. Chem.* **2007**, *119*, 1652–1654; *Angew. Chem. Int. Ed.* **2007**, *46*, 1627–1629.

[26] L. Ackermann, *Org. Lett.* **2005**, *7*, 439–442.

[27] L. T. Kaspar, L. Ackermann, *Tetrahedron* **2005**, *61*, 11311–11316.

[28] For applications of this methodology, see: a) P.-Y. Yao, Y. Zhang, R. P. Hsung, K. Zhao, *Org. Lett.* **2008**, *10*, 4275–4278; b) R. Sanz, M. P. Castroviejo, V. Guilarte, A. Perez, F. J. Fananas, *J. Org. Chem.* **2007**, *72*, 5113–5118; c) Z.-Y. Tang, Q.-S. Hu, *Adv. Synth. Catal.* **2006**, *348*, 846–850.

[29] D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450–1460.

[30] S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.

[31] K. Kunz, U. Scholz, *Synlett* **2003**, 2428–2439.

[32] For representative recent examples of copper-catalyzed heteroarene syntheses, see: a) R. C. Hodgkinson, J. Schulz, M. C. Willis, *Org. Biomol. Chem.* **2009**, DOI: 10.1039/b817254d; b) R. D. Viirre, G. Evindar, R. A. Batey, *J. Org. Chem.* **2008**, *73*, 3452–3459; c) A. Minatti, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2721–2724; d) R. Martín, A. Cuenca, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 5521–5524; e) Y. Chen, X. Xie, D. Ma, *J. Org. Chem.* **2007**, *72*, 9329–9334; f) J. Yuen, Y.-Q. Fang, M. Lautens, *Org. Lett.* **2006**, *8*, 653–656; g) C.-y. Chen, P. G. Dormer, *J. Org. Chem.* **2005**, *70*, 6964–6967, and references cited therein.

[33] For a related elegant copper-catalyzed domino synthesis of substituted pyrroles and pyrazoles, see: R. Martín, M. R. Rivero, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 7237–7240; *Angew. Chem. Int. Ed.* **2006**, *45*, 7079–7082.

[34] A. A. Kelkar, N. M. Patil, R. V. Chaudhari, *Tetrahedron Lett.* **2002**, *43*, 7143–7146.

[35] B. Schlummer, U. Scholz, in: *Modern Arylation Methods*, (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**, pp 69–120.

[36] D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361.

[37] S. P. Nolan, *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH, Weinheim, **2006**.

[38] W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342–1363; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309.

[39] D. Ma, Y. Zhang, J. Yao, S. Wu, F. Tao, *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467.

[40] J. Folkman, *Nature Med.* **1995**, *1*, 27–31.

[41] J. Folkman, *N. Engl. J. Med.* **1995**, *333*, 1757–1763.

[42] P. Traxler, *Expert Opin. Ther. Targets* **2003**, *7*, 215–234.

[43] G. D. Yancopoulos, S. Davis, N. W. Gale, J. S. Rudge, S. J. Wiegand, J. Holash, *Nature* **2000**, *407*, 242–248.

[44] P. Carmeliet, R. K. Jain, *Nature* **2000**, *407*, 249–257.

[45] T. Veikkola, M. Karkkainen, L. Claesson-Welsh, K. Alitalo, *Cancer Res.* **2000**, *60*, 203–212.

[46] K. A. Thomas, *J. Biol. Chem.* **1996**, *271*, 603–606.

[47] J. T. Kuethe, A. Wong, I. W. Davies, *Org. Lett.* **2003**, *5*, 3975–3978.

[48] M. E. Fraley, K. L. Arrington, C. A. Buser, P. A. Ciecko, K. E. Coll, C. Fernandes, G. D. Hartman, W. F. Hoffman, J. J. Lynch, R. C. McFall, K. Rickert, R.

Singh, S. Smith, K. A. Thomas, B. K. Wong, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 351–355.
[49] A. Wong, J. T. Kuethe, I. W. Davies, D. L. Hughes, *J. Org. Chem.* **2004**, *69*, 7761–7764.
[50] J. F. Payack, E. Vazquez, L. Matty, M. H. Kress, J. McNamara, *J. Org. Chem.* **2005**, *70*, 175–178.
[51] J. T. Kuethe, A. Wong, C. Qu, J. Smitrovich, I. W. Davies, D. L. Hughes, *J. Org. Chem.* **2005**, *70*, 2555–2567.
[52] a) S. Huang, R. M. Garbaccio, M. E. Fraley, J. Steen, C. Kreatsoulas, G. Hartman, S. Stirdivant, B. Drakas, K. Rickert, E. Walsh, K. Hamilton, C. A. Buser, J. Hardwick, X. Mao, M. Abrams, S. Beck, W. Tao, R. Lobell, L. Sepp-Lorenzino, Y. Yan, M. Ikuta, J. Z. Murphy, V. Sardana, S. Munshi, L. Kuo, M. Reilly, E. Mahan, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5907–5912; b) M. E. Fraley, J. T. Steen, E. J. Brnardic, K. L. Arrington, K. L. Spencer, B. A. Hanney, Y. Kim, G. D. Hartman, S. M. Stirdivant, B. A. Drakas, K. Rickert, E. S. Walsh, K. Hamilton, C. A. Buser, J. Hardwick, W. Tao, S. C. Beck, X. Mao, R. B. Lobell, L. Sepp-Lorenzino, Y. Yan, M. Ikuta, S. K. Munshi, L. C. Kuoc, C. Kreatsoulas, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6049–6053.
[53] Y.-Q. Fang, R. Karisch, M. Lautens, *J. Org. Chem.* **2007**, *72*, 1341–1346.
[54] S. S. Palimkar, V. S. More, P. H. Kumar, K. V. Srinivasan, *Tetrahedron* **2007**, *63*, 12786–12790.
[55] Z. Wang, J. Wu, *Tetrahedron* **2008**, *64*, 1736–1742.
[56] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *50*, 4467–4470.
[57] C. Macleod, G. J. McKiernan, E. J. Guthrie, L. J. Farrugia, D. W. Hamprecht, J. Macritchie, R. C. Hartley, *J. Org. Chem.* **2003**, *68*, 387–401.