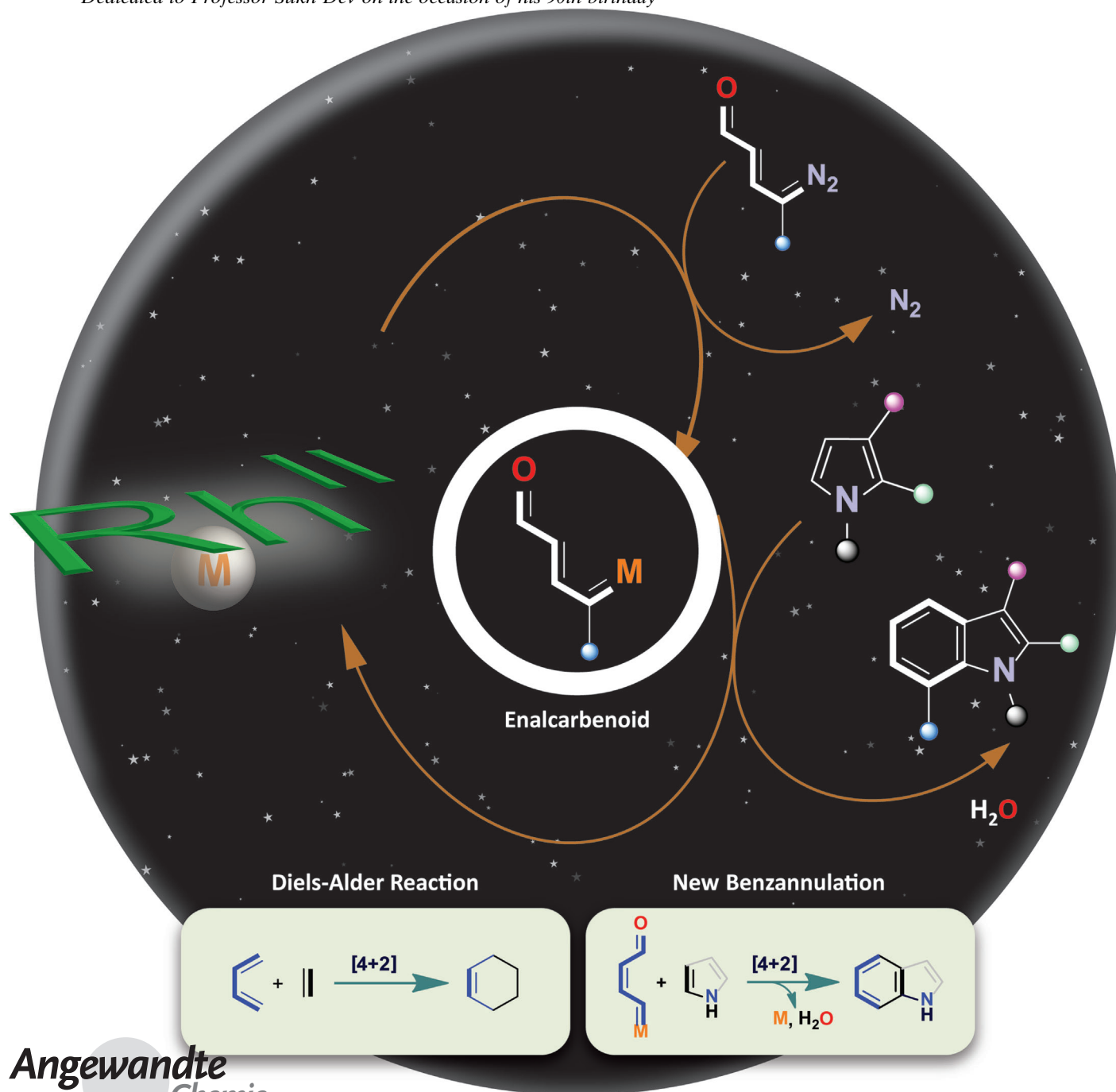




Rhodium Enalcarbenoids: Direct Synthesis of Indoles by Rhodium(II)-Catalyzed [4+2] Benzannulation of Pyrroles**

Sudam Ganpat Dawande, Vinaykumar Kanchupalli, Jagadeesh Kalepu, Haribabu Chennamsetti, Bapurao Sudam Lad, and Sreenivas Katukojvala*

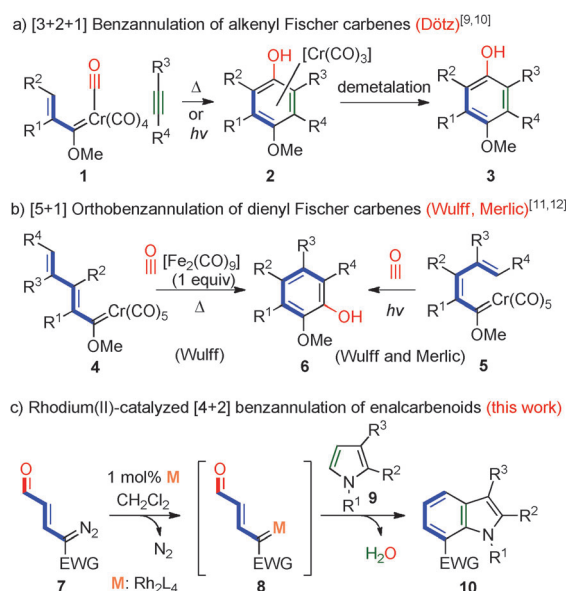
Dedicated to Professor Sukh Dev on the occasion of his 90th birthday



Abstract: Disclosed herein is the design of an unprecedented electrophilic rhodium enalcarbenoid which results from rhodium(II)-catalyzed decomposition of a new class of enaldiazo compounds. The synthetic utility of these enalcarbenoids has been successfully demonstrated in the first transition-metal-catalyzed [4+2] benzannulation of pyrroles, thus leading to substituted indoles. The new benzannulation has been applied to the efficient synthesis of the natural product leiocarpone as well as a potent adipocyte fatty-acid binding protein inhibitor.

Indoles are a very important structural motifs which are present in diverse natural products, pharmaceuticals, fine-chemicals, and materials.^[1,2] Hence, development of new methodologies for functionalized indoles continues to be an active research area.^[3] The classical methods include Fischer, Bartoli, and Larock syntheses.^[4] The majority of the recent methodologies involve transition-metal-catalyzed annulations onto an appropriately functionalized benzene ring.^[5] In contrast, transition-metal-catalyzed annulations onto pyrrole rings are scarce, not general, or can consist of a multistep synthesis.^[6] Hence, development of efficient catalytic methodologies for the direct benzannulation of pyrroles would be highly valuable.

Benzannulation is a fundamentally significant reaction for the formation of substituted benzenes. For the past few decades, several elegant benzannulation strategies, including transition-metal-mediated reactions, have been developed for functionalized benzene and fused benzene derivatives.^[7,8] Among these strategies, the Dötz [3+2+1] benzannulation of alkenyl Fischer carbene complexes (**1**) with alkynes is a highly versatile method for the functionalized 4-alkoxy phenol derivatives **2** and **3** (Scheme 1 a).^[9,10] In contrast, the complementary Wulff and Merlic [5+1] orthobenzannulation of the dienylyl Fischer carbene complexes **4** and **5** delivers valuable *o*-alkoxy phenol derivatives (**6**; Scheme 1 b).^[11,12] Despite their great synthetic utility, these benzannulations are not catalytic, involve stoichiometric chromium carbene complexes, and require carbon monoxide as one-carbon reactant from either a metal template or as a reagent. Thus, development of catalytic versions of these benzannulations, in which the use of stoichiometric carbene complexes and carbon monoxide are avoided, would be highly useful. In this context we have designed a conceptually new class of enaldiazo compounds (**7**) consisting of a four-carbon unit embedded within an alkenyl and carbonyl moiety (Scheme 1 c). We envisioned that the electrophilic diaceptor^[13] enalcarbenoid **8**, generated by transition-metal-catalyzed

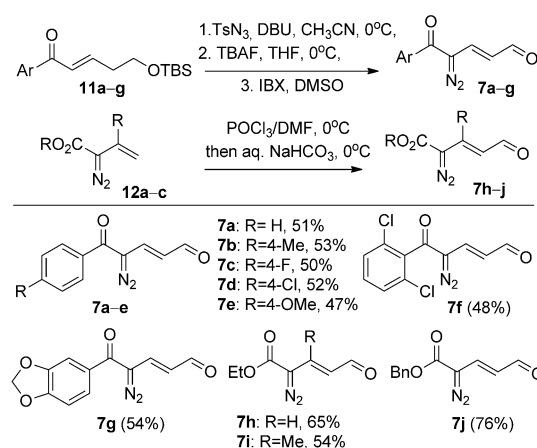


Scheme 1. Benzannulation of carbene complexes. EWG = electron-withdrawing group.

decomposition of the diazo compound **7**, would serve as a four-carbon reacting partner for unique catalytic annulation reactions. Herein, we report the realization of the first catalytic [4+2] benzannulation of rhodium enalcarbenoids (**8**; $M = Rh_2L_4$) with the pyrroles **9**, thus leading to the direct synthesis of valuable substituted indoles (**10**).^[14]

As shown in Scheme 2, a variety of enaldiazo ketones (**7a–g**) and esters (**7h–j**) were prepared.^[15] Enaldiazo ketones were obtained in three steps from the aryl enones **11** and involved diazotransfer, deprotection, and oxidation reactions. In contrast, the enaldiazo esters **7h–j** were prepared by formylation of the known vinyldiazo esters **12**^[16] using the Vilsmeier reagent.

Our studies on the enaldiazo compounds **7** were initiated by rhodium(II)-catalyzed reactions with pyrroles.^[17,18] To our



Scheme 2. Design and synthesis of new enaldiazo compounds.^[15] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N,N*-dimethylformamide, DMSO = dimethylsulfoxide, IBX = 2-iodoxybenzoic acid, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

[*] S. G. Dawande, V. Kanchupalli, J. Kalepu, H. Chennamsetti, B. S. Lad, Dr. S. Katukojvala
Department of Chemistry
Indian Institute of Science Education & Research
Bhopal, Madhya Pradesh 462066 (India)
E-mail: sk@iiserb.ac.in
Homepage: <http://home.iiserbhopal.ac.in/~sk/>

[**] We are grateful for the financial support from IISER Bhopal and the Department of Science and Technology. We thank Dr. S. Konar and P. Srinivasulu for X-ray crystal structure determination.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201400161>.

delight, when a 0.1 M solution of **7a** (0.1 mmol, 1 equiv) in dichloromethane (CH_2Cl_2) was added slowly over a 1 hour period to a CH_2Cl_2 solution (1 mL) of pyrrole (0.15 mmol) and 1 mol % $[\text{Rh}_2(\text{OAc})_4]$ at room temperature, the indole **13** was obtained in 62 % yield. The yield was improved to 71 % with 1:1 ratio of pyrrole and diazo substrate. Use of slight excess of the aldehyde (1.2 equiv) gave an optimum yield of 89 %. Interestingly, the benzannulation proceeded with complete regioselectivity, thus leading to 7-substituted indole.^[15] Encouraged by this exciting result we screened several rhodium(II) catalysts and solvents for the reaction (Table 1). All rhodium(II) catalysts tested are effective, but the best results were obtained with 1 mol % $[\text{Rh}_2(\text{OAc})_4]$ in CH_2Cl_2 . It is noteworthy that even 0.1 mol % $[\text{Rh}_2(\text{OAc})_4]$ was sufficient for the efficient benzannulation at larger scale (entry 11).

Table 1: Optimization of benzannulation.^[a]

Entry	$[\text{Rh}_2\text{L}_4]$	Mol %	Solvent	Yield [%] ^[b]
1	$[\text{Rh}_2(\text{OAc})_4]$	1	CH_2Cl_2	89
2	$[\text{Rh}_2(\text{Oct})_4]$	1	CH_2Cl_2	68
3	$[\text{Rh}_2(\text{esp})_4]$	1	CH_2Cl_2	58
4	$[\text{Rh}_2(\text{TFA})_4]$	1	CH_2Cl_2	48
5	$[\text{Rh}_2\{(R)\text{-dosp}\}]_4]$	1	CH_2Cl_2	61
6	$[\text{Rh}_2(\text{OAc})_4]$	1	CHCl_3	80
7	$[\text{Rh}_2(\text{OAc})_4]$	1	Toluene	62
8	$[\text{Rh}_2(\text{OAc})_4]$	1	$\text{C}_2\text{H}_4\text{Cl}_2$	64
9	$[\text{Rh}_2(\text{OAc})_4]$	0.1	CH_2Cl_2	81
10	$[\text{Rh}_2(\text{OAc})_4]$	1.5	CH_2Cl_2	72
11	$[\text{Rh}_2(\text{OAc})_4]$	0.1	CH_2Cl_2	87 ^[c]

[a] Reaction conditions: **7a**/pyrrole = 0.12:0.1 mmol; a solution of **7a** (1 mL) was added over 1 h to a solution of pyrrole and rhodium(II) catalyst (1 mL) at RT, and stirred for an additional 2 h. [b] Yield of isolated product. [c] Reaction carried out with 1 mmol of pyrrole. dosp = (*N*-dodecylbenzenesulfonyl)proline, esp = $\alpha,\alpha',\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid, TFA = trifluoroacetate.

With the optimized reaction conditions, the generality of the benzannulation was tested with various enaldiazo ketones (**7a–g**) and pyrroles (Table 2). Pyrrole gave excellent yields of the indole products **14–19**^[19] (87–92 %) with the enaldiazo ketones **7a–g**, thus indicating that the electronic and steric nature of the aryl group in diazo ketones did not have a noticeable impact on the benzannulation. Both 2- and 3-alkyl-substituted pyrroles participated efficiently in the benzannulation, thus leading to the 2-methyl indoles **20–22** in 81–90 % yield and 3-benzyl indole **23** in 58 % yield.^[19] The electron-deficient 3-acyl pyrroles smoothly gave high yields of the biologically relevant 3-acylindoles derivatives **24–26** in 81–85 % yield.^[20,21] Even 2,3-disubstitution on pyrrole facilitated the benzannulation, thus resulting in very good yields of the densely functionalized indoles **27** (83 %) and **28** (80 %). When the benzannulation was protected from light, the highly unstable 3-chloropyrrole gave good yields of the 3-chloroindole derivatives **29** (68 %) and **30** (65 %), which are suitable

Table 2: Rhodium(II)-catalyzed [4+2] benzannulation of enaldiazo ketones with pyrroles.^[a]

14 (91%)	15 (89%)
16 (92%)	17 (90%)
18 (87%)	19 (92%)
20 (90%)	21 (85%)
22 (81%)	23 (58%)
24 (81%)	25 (84%)
26 (85%)	27 (83%)
28 (80%)	
29 (68%)	30 (65%)
31 (71%) ^[b]	32 (66%) ^[b]
33 (69%) ^[b]	34 (65%) ^[b]
35 (72%)	36 (65%) ^[b]

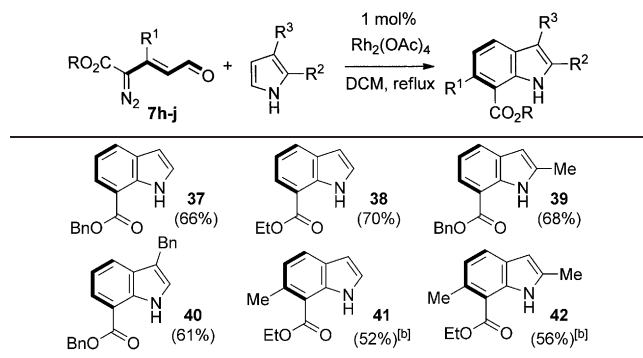
[a] 0.24 mmol of **7** in CH_2Cl_2 was added over 2 h to a solution of *N*-H pyrrole and $[\text{Rh}_2(\text{OAc})_4]$ (0.2:0.002 mmol), and was then stirred for an additional 2 h. [b] 0.6 mmol of **7** added over 5 h. Cbz = benzyloxycarbonyl.

substrates for cross-coupling reactions. The *N*-substituted pyrroles required longer reaction times and an excess amount of the diazo partner (3 equiv) to give good yields of the indoles **31–34** (65–71 %). This outcome could be attributed to the steric hindrance at the 2-position of the pyrrole ring. An interesting example is the preferential benzannulation over *N*-H insertion of 2-(pyrrol-2-yl)ethanaminecarbamates, a reaction which gave good yields of the valuable isotryptamine derivatives **35** (72 %) and **36** (65 %).

In contrast to the enaldiazo ketones **7a–g**, benzannulation reaction with the enaldiazo esters **7h–j** was sluggish at room

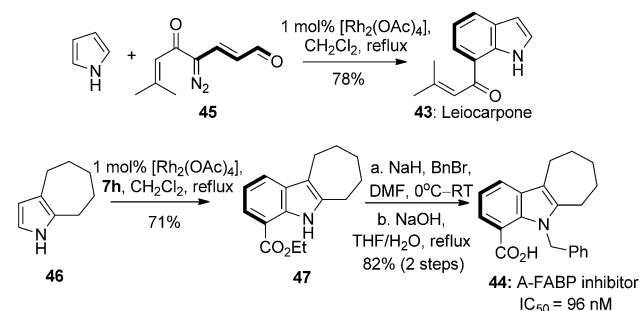
temperature as they proceeded via an unstable intermediate.^[15] However, the reaction was efficient with excess diazo substrate (2.5 equiv) at reflux conditions in CH₂Cl₂, and gave the indoles **37–42** in 52–70 % yield (Table 3). To our delight the reaction tolerated methyl substitution on the enaldiazo ester **7i**, which gave decent yields of the valuable 6-methyl indole derivatives **41** (52 %) and **42** (56 %) when using an excess of diazo substrate (4 equiv).

Table 3: Rhodium(II)-catalyzed [4+2] benzannulation of enaldiazo esters with pyrroles.^[a]



[a] 0.5 mmol of **7** in CH₂Cl₂ was added over 4 h to a refluxing solution of pyrrole and [Rh₂(OAc)₄] (0.2:0.002 mmol) in CH₂Cl₂ and stirred for additional 2 h. [b] 0.8 mmol of **7** added over 7 h.

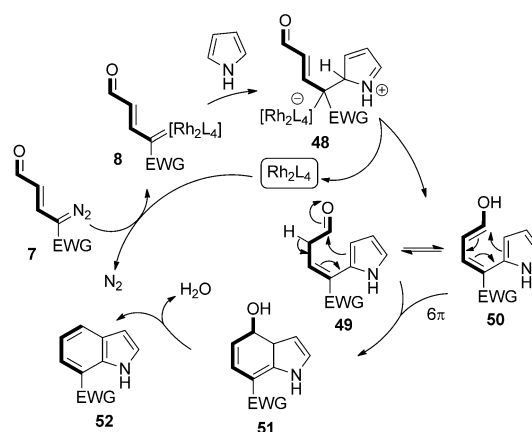
The synthetic utility of benzannulation was demonstrated with a short synthesis of the 7-substituted indole natural product leiocarpone (**43**),^[22] as well as a potent and selective adipocyte fatty-acid binding protein (A-FABP) inhibitor (**44**; Scheme 3).^[23] Thus, direct benzannulation of pyrrole with the



Scheme 3. Synthetic applications of benzannulation.

enaldiazo ketone **45** gave leiocarpone (**43**) in 78 % yield. In contrast benzannulation of the cycloheptapyrrole **46** with **7h** gave the indole **47** (71 % yield), which upon N-benylation and subsequent saponification gave the A-FABP inhibitor **44** (82 % for two steps).

As shown in Scheme 4, a catalytic cycle for the benzannulation was proposed. The initial step involves rhodium(II)-catalyzed generation of the enalcarbenoid **8** from the diazo compound **7**. Subsequent regioselective functionalization at the 2-position of the pyrrole with **8** leads to the zwitterion **48**. Proton transfer and subsequent intramolecular cyclization of



Scheme 4. Proposed mechanism of [4+2] benzannulation.

48 via **49**^[24] or **50** delivers the alcohol **51**. Subsequent dehydration of **51** results in the formation of the indole **52**.

In summary we have designed a new class of enaldiazo ketones and esters. The unprecedented rhodium enalcarbenoids derived from these diazo compounds have been employed in the first direct catalytic [4+2] benzannulation of pyrroles, thus leading to substituted indoles. In contrast to the Dötz, Wulff, and Merlic benzannulations, which uses stoichiometric Fischer carbenes, our new benzannulation involves catalytically generated rhodium enalcarbenoids. The synthetic utility of the benzannulation was demonstrated with the highly efficient one step synthesis of leiocarpone as well as a short synthesis of a potent and selective adipocyte fatty-acid binding protein (A-FABP) inhibitor. Studies are ongoing with regard to the mechanistic aspects of the benzannulation and its applications. We hope that the new class of enaldiazo compounds, enalcarbenoids, and the benzannulation reaction will find wide applications in synthetic chemistry.

Received: January 7, 2014

Published online: March 3, 2014

Keywords: annulation · carbenes · diazo compounds · heterocycles · rhodium

- [1] a) N. K. Kaushik, N. Kaushik, P. Attri, P. N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620; b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489; c) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; d) M. T. Hamann, G. Waseem, *Life Sci.* **2005**, *78*, 442; e) U. Pindur, T. Lemster, *Curr. Med. Chem.* **2001**, *8*, 1681.
- [2] a) W. Zhu, Y. Wu, S. Wang, W. Li, X. Li, J. Chen, Z.-S. Wang, H. Tian, *Adv. Funct. Mater.* **2011**, *21*, 756; b) Q. Ye, Y.-H. Li, Y.-M. Song, X.-F. Huang, R.-G. Xiong, Z. Xue, *Inorg. Chem.* **2005**, *44*, 3618.
- [3] a) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29; b) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195; c) K. Krüger née Alex, A. Tillack, M. Bellar, *Adv. Synth. Catal.* **2008**, *350*, 2153; d) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875; e) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; f) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**,

- 103, 893; g) H. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, 102, 4303; h) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045; i) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**.
- [4] 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) G. Bartoli, F. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, 30, 2129; d) G. Bartoli, M. Bosco, R. Dalpozzo, *J. Chem. Soc.* **1991**, 2757; e) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, 104, 2285; f) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, 113, 6689.
- [5] Representative recent examples involving transition metals: a) T. Miura, Y. Funakoshi, M. Murakami, *J. Am. Chem. Soc.* **2014**, 136, 2272; b) D. Shu, W. Song, X. Li, W. Tang, *Angew. Chem.* **2013**, 125, 3319; *Angew. Chem. Int. Ed.* **2013**, 52, 3237; c) D. Shan, Y. Gao, Y. Jia, *Angew. Chem.* **2013**, 125, 5002; *Angew. Chem. Int. Ed.* **2013**, 52, 4902; d) B. V. S. Reddy, M. R. Reddy, Y. G. Rao, J. S. Yadav, B. Sridhar, *Org. Lett.* **2013**, 15, 464; e) Y. Wang, L. Liu, L. Zhang, *Chem. Sci.* **2013**, 4, 739; f) J. S. Alford, J. E. Spangler, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, 135, 11712; g) B. Liu, C. Song, C. Sun, S. Zhou, J. Zhu, *J. Am. Chem. Soc.* **2013**, 135, 16625; h) B. Anxionnat, D. G. Pardo, G. Ricci, K. Rossen, J. Cossy, *Org. Lett.* **2013**, 15, 3876; i) Q. Nguyen, T. Nguyen, T. G. Driver, *J. Am. Chem. Soc.* **2013**, 135, 620; j) M. Chiarucci, R. Mocchi, L.-D. Syntrivianis, G. Cera, A. Mazzanti, M. Bandini, *Angew. Chem.* **2013**, 125, 11050; *Angew. Chem. Int. Ed.* **2013**, 52, 10850; k) A. Frischmuth, P. Knochel, *Angew. Chem.* **2013**, 125, 10268; *Angew. Chem. Int. Ed.* **2013**, 52, 10084.
- [6] a) K. Hayashi, K. Yoshida, A. Yanagisawa, *J. Org. Chem.* **2013**, 78, 3464; b) K. Yoshida, K. Hayashi, A. Yanagisawa, *Org. Lett.* **2011**, 13, 4762; c) N. Asao, H. Aikawa, *J. Org. Chem.* **2006**, 71, 5249; d) M. Iwasaki, Y. Kobayashi, J.-P. Li, H. Matsuzaka, Y. Ishii, M. Hidai, *J. Org. Chem.* **1991**, 56, 1922.
- [7] a) *Transition-Metal-Mediated Aromatic Ring Construction* (Ed.: K. Tanaka), Wiley, Hoboken, **2013**; b) "Cycloaddition and Benzannulation Approaches to Functionalised Aromatic Compounds": *Tetrahedron* **2008**, 64, pp. 757–968 (Ed.: J. P. A. Harrity); c) S. Kotha, S. Misra, S. Halder, *Tetrahedron* **2008**, 64, 10775; d) M. Rubin, A. W. Sromek, V. Gevorgyan, *Synlett* **2003**, 2265; e) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, 100, 2901; f) A. de Meijere, H. Schirmer, M. Duetsch, *Angew. Chem.* **2000**, 112, 4124; *Angew. Chem. Int. Ed.* **2000**, 39, 3964; g) R. L. Danheiser, R. G. Brisbois, J. J. Kowalczyk, R. F. Miller, *J. Am. Chem. Soc.* **1990**, 112, 3093; h) R. L. Danheiser, S. K. Gee, *J. Org. Chem.* **1984**, 49, 1672; i) K. P. C. Vollhardt, *Angew. Chem.* **1984**, 96, 525; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 539.
- [8] For selected recent examples, see: a) P. Gao, J. Liu, Y. Wei, *Org. Lett.* **2013**, 15, 2872; b) S. Zhu, Y. Xiao, Z. Guo, H. Jiang, *Org. Lett.* **2013**, 15, 898; c) J. Zheng, Y. Huang, Z. Li, *Org. Lett.* **2013**, 15, 5064; d) O. V. Zatolochnaya, V. Gevorgyan, *Org. Lett.* **2013**, 15, 2562; e) F. Jafarpour, H. Hazrati, S. Nouraldinmoussa, *Org. Lett.* **2013**, 15, 3816; f) J. D. Kirkham, R. J. Butlin, J. P. A. Harrity, *Angew. Chem.* **2012**, 124, 6508; *Angew. Chem. Int. Ed.* **2012**, 51, 6402; g) A.-L. Auvinet, J. P. A. Harrity, *Angew. Chem.* **2011**, 123, 2821; *Angew. Chem. Int. Ed.* **2011**, 50, 2769; h) A. Matsumoto, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, 133, 6557; i) J. Barluenga, A. Gomez, J. Santamaria, M. Tomas, *J. Am. Chem. Soc.* **2009**, 131, 14628.
- [9] a) K. H. Dötz, J. Stendel, Jr., *Chem. Rev.* **2009**, 109, 3227; b) A. Minatti, K. H. Dötz, *Top. Organomet. Chem.* **2004**, 13, 123; c) K. H. Dötz, P. Tomuschat, *Chem. Soc. Rev.* **1999**, 28, 187; d) W. D. Wulff in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1990**; e) W. D. Wulff, P.-C. Tang, K.-S. Chan, J. S. McCallum, D. C. Yang, S. R. Gilbertson, *Tetrahedron* **1985**, 41, 5813.
- [10] a) K. H. Dötz, *Angew. Chem.* **1984**, 96, 573; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 587; b) K. H. Dötz, *Angew. Chem.* **1975**, 87, 672; *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 644.
- [11] a) Y. Lian, W. D. Wulff, *J. Am. Chem. Soc.* **2005**, 127, 17162; b) W. D. Wulff in *Advances in Metal-Organic Chemistry*, Vol. 1 (Ed.: L. S. Liebeskind), JAI, Greenwich, CT, **1989**.
- [12] a) C. A. Merlic, D. Xu, *J. Am. Chem. Soc.* **1991**, 113, 7418; for synthesis of 2-aminophenols see: b) C. A. Merlic, E. E. Burns, D. Xu, S. Y. Chen, *J. Am. Chem. Soc.* **1992**, 114, 8722; For other variations see: c) M. Franck-Neumann, P. Geoffroy, A. Winling, *Synlett* **1995**, 341; d) J. Barluenga, F. Aznar, M. A. Palomero, S. Barluenga, *Org. Lett.* **1999**, 1, 541.
- [13] For a classification of various stabilized carbenoids, see: H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, 36, 1109.
- [14] For recent reports on rhodium(II)-catalyzed synthesis of indoles via 1-sulfonyl-1,2,3-triazoles, see Refs. [5a] and [5f].
- [15] See the Supporting Information for experimental details and characterization.
- [16] a) A. M. Jadhav, V. V. Pagar, R.-S. Liu, *Angew. Chem.* **2012**, 124, 11979; *Angew. Chem. Int. Ed.* **2012**, 51, 11809; b) V. V. Pagar, A. M. Jadhav, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, 133, 20728; c) H. M. L. Davies, P. W. Hougland, W. R. Cantrell, Jr., *Synth Commun.* **1992**, 22, 971.
- [17] General references for transition-metal-catalyzed reactions of diazo compounds: a) Z. Zhang, J. Wang, *Tetrahedron* **2008**, 64, 6577; b) M. P. Doyle, M. A. McKervy, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**; c) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, 98, 911; d) T. Ye, M. A. McKervy, *Chem. Rev.* **1994**, 94, 1091; e) M. P. Doyle, *Chem. Rev.* **1986**, 86, 919.
- [18] Selected references for reactions of pyrroles with metal carbenoids: see Ref. [13] and a) D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma, W. Hu, *Angew. Chem.* **2013**, 125, 13598; *Angew. Chem. Int. Ed.* **2013**, 52, 13356; b) J. Barluenga, G. Lonzi, M. Tomas, L. A. Lopez, *Chem. Eur. J.* **2013**, 19, 1573; c) Y. Lian, H. M. L. Davies, *Org. Lett.* **2012**, 14, 1934; d) J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, 2, 457; e) Y. Lian, H. M. L. Davies, *Org. Lett.* **2010**, 12, 924; f) R. P. Reddy, H. M. L. Davies, *J. Am. Chem. Soc.* **2007**, 129, 10312.
- [19] CCDC 971585 (**16**) and 971587 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [20] Y.-S. Wu, M. S. Coumar, J.-Y. Chang, H.-Y. Sun, F.-M. Kuo, C.-C. Kuo, Y.-J. Chen, C.-Y. Chang, C.-L. Hsiao, J.-P. Liou, C.-P. Chen, H.-T. Yao, Y.-K. Chiang, U.-K. Tan, C.-T. Chen, C.-Y. Chu, S.-Y. Wu, T.-K. Yeh, C.-Y. Lin, H.-P. Hsieh, *J. Med. Chem.* **2009**, 52, 4941.
- [21] For the recent synthesis of 3-acylindoles, see: a) K. C. Coffman, T. A. Palazzo, T. P. Hartley, J. C. Fetting, D. J. Tantillo, M. J. Kurth, *Org. Lett.* **2013**, 15, 2062; b) A. Gogoi, S. Guin, S. K. Rout, B. K. Patel, *Org. Lett.* **2013**, 15, 1802; c) T.-S. Jiang, G.-W. Wang, *Org. Lett.* **2013**, 15, 788; d) L. Yu, P. Li, L. Wang, *Chem. Commun.* **2013**, 49, 2368; e) X.-F. Xia, L.-L. Zhang, X.-R. Song, Y.-N. Niu, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2013**, 49, 1410; f) Y. Ma, J. You, F. Song, *Chem. Eur. J.* **2013**, 19, 1189; g) Y. Li, D. Xue, W. Lu, X. Fan, C. Wang, J. Xiao, *RSC Adv.* **2013**, 3, 11463.
- [22] a) J. E. Saxton, *Nat. Prod. Rep.* **1992**, 9, 393; b) F. D. Monache, R. D. Benedetto, M. A. De Moraes e Souza, P. Sandor, *Gazz. Chim. Ital.* **1990**, 120, 387; c) M. P. Moyer, J. F. Shiurba, H. Rapoport, *J. Org. Chem.* **1986**, 51, 5106.
- [23] T. Barf, F. Lahmann, K. Hammer, S. Haile, E. Axen, C. Medina, J. Uppenberg, S. Svensson, L. Rondahl, T. Lundback, *Bioorg. Med. Chem. Lett.* **2009**, 19, 1745.
- [24] Observed by NMR studies. See the Supporting Information.