Pergamon

Tetrahedron 56 (2000) 4733–4737

TETRAHEDRON

Transition Metal Complexes in Organic Synthesis. Part 61:[1] Convergent Synthesis of Indolo[2,3-*b*]carbazole by an Iron-Mediated Bidirectional Annulation of Two Indole Rings

Hans-Joachim Knölker* and Kethiri R. Reddy

Institut für Organische Chemie, Universität Karlsruhe, Richard-Willstätter-Allee, D-76131 Karlsruhe, Germany

Received 12 April 2000; accepted 29 April 2000

Abstract—A highly convergent synthesis provides indolo[2,3-*b*]carbazole in two steps and 36% overall yield from commercial *m*-phenylenediamine by a double iron-mediated consecutive C–C and C–N bond formation featuring the first double iron-mediated arylamine cyclization.

The promising biological activities of naturally occurring carbazole alkaloids led to a considerable interest in the chemistry of 9*H*-carbazoles and induced the development of novel methodologies for their synthesis.[2] The indolo[2,3-*a*]carbazole framework is found in the antitumor active alkaloids staurosporine, K-252a, and rebeccamycin,[3] which due to their pharmacological importance became attractive targets for total synthesis.[4] Altogether there exist five different pentacyclic indolocarbazole isomers and synthetic routes were described to all of the five parent ring systems **1**–**5** (Fig. 1).[5–7] However, these methods often require multi-step syntheses and in some cases harsh reaction conditions led to low overall yields. Therefore, novel efficient procedures leading to highly convergent synthetic routes for this class of compounds are still under investigation.

For the parent indolo[2,3-*b*]carbazole **2** only two syntheses were described,[5,6] prior to our work.[8] The first synthesis by Grotta et al. in 1961 used a catalytic cyclodehydrogenation of *N*,*N*′-diphenyl-*m*-phenylenediamine at 500°C in the vapor phase to afford compound **2** in 3% yield.[5] In 1992 Müllen et al. reported a second synthesis using a reductive ring closure of 2,4-dinitro-1,5-diphenylbenzene as the key-step.[6]

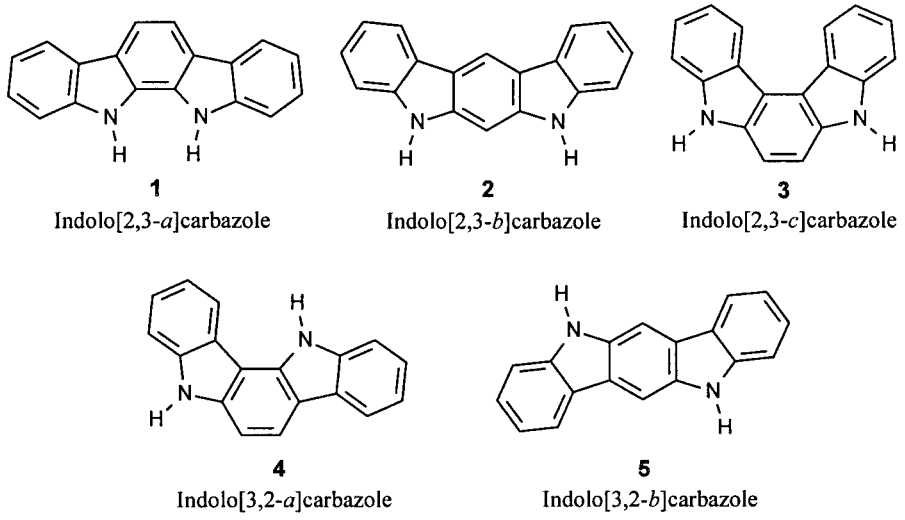
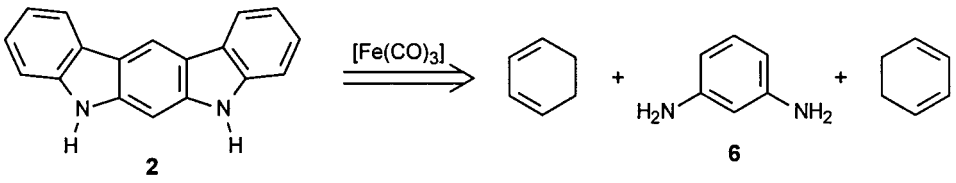


Figure 1.

Keywords: indolocarbazoles; electrophilic substitution; oxidative cyclization; tricarbonyliron complexes.
* Corresponding author. Tel.: +49-721-608-2902; fax: +49-721-698-529; e-mail: knoe@ochhades.chemie.uni-karlsruhe.de

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00381-1



Scheme 1.

Over the past decade we developed efficient total syntheses for a large number of highly substituted biologically active carbazole alkaloids using an iron-mediated construction of the carbazole framework.[9,10] For the synthesis of indolo[2,3-*b*]carbazole **2** we envisaged a highly convergent synthesis by using our methodology for a bidirectional annulation of the two indole rings at a central *m*-phenylenediamine **6** (Scheme 1). In this paper, we wish to present full details for the synthesis of indolo[2,3-*b*]carbazole **2** by the first double iron-mediated consecutive C–C and C–N bond formation.[8]

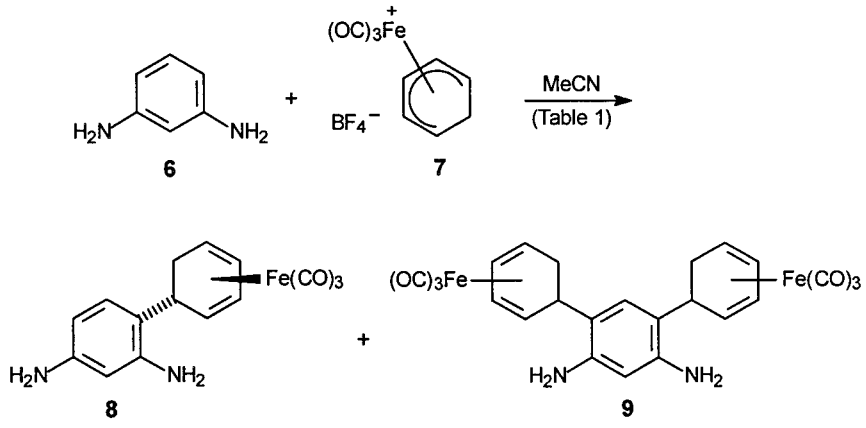
For the convergent synthesis of indolo[2,3-*b*]carbazole **2** we required the dinuclear iron complex **9**, which can be prepared by a twofold electrophilic substitution of *m*-phenylenediamine **6** and the iron complex salt **7** (Scheme 2). Birch et al. reported that the reaction of 1.5 equiv. of **6** with **7** in acetonitrile for 10 min at room temperature afforded only the disubstituted product **9** in 72% yield.[11] We reinvestigated the electrophilic substitution of *m*-phenylenediamine **6** with the iron complex salt **7** in more detail by variation of the reaction parameters (Table 1). Reaction of equimolar amounts of **6** and **7** provided almost equal amounts of the mono and dinuclear complexes **8** and **9**. A gradual increase of the amount of the iron complex salt **7** favored the formation of the dinuclear complex **9**. Finally, using 2.2 equiv. of the iron complex salt **7** we obtained the dinuclear complex **9** almost quantitatively as a mixture of two diastereoisomers in a ratio of 1:1. The melting point of complex **9** (156–158°C) is higher than previously reported (136–138°C).[11]

The projected key-step of our synthesis is the double iron-mediated arylamine cyclization of the dinuclear complex **9** to indolo[2,3-*b*]carbazole **2**. However, several reagents previously applied to the iron-mediated arylamine cyclization (very active manganese dioxide and ferricenium hexafluorophosphate/sodium carbonate)[9,10] led only to decomposition of the starting material. We then used commercial manganese dioxide,[12] which was additionally activated by azeotropic removal of water.[13] Thus, oxidation of complex **9** with 10 mass equivalents of this activated manganese dioxide in benzene at room temperature for 3 days afforded indolo[2,3-*b*]carbazole **2** in only 8% yield.

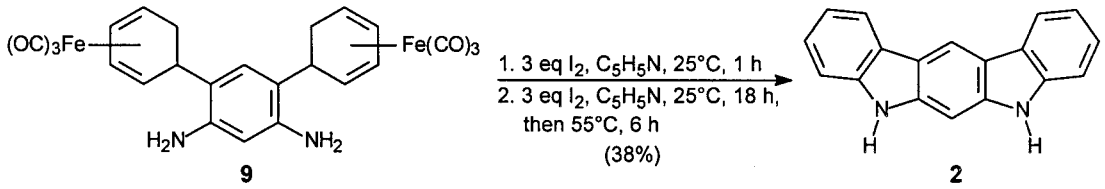
In search of other reagents for the oxidative cyclization we tested iodine in pyridine.[11,14] Usually iodine leads to demetalation of tricarbonyl(η^4-cyclohexa-1,3-diene)iron complexes, but in some cases it has been used to achieve an iron-mediated arylamine cyclization with concomitant cyclization to the aromatized 9*H*-carbazole derivatives in moderate yields.[14,15] Recently, we applied the iron-mediated arylamine cyclization by oxidation with iodine to the first total synthesis of the furo[3,2-*a*]carbazole alkaloid furostifoline.[16] The oxidation of complex **9** using the standard conditions (pyridine, 90°C) led only to complete decomposition of the starting material. However, the course of this oxidation can be controlled by a very careful fine-tuning of the reaction conditions. Treatment of complex **9** with 3 equiv. of iodine in pyridine at room temperature led to complete disappearance of the starting material in favor of a less polar compound which is not identical with indolo[2,3-*b*]carbazole **2** (TLC analysis). Prolonged stirring at room temperature or heating at 90°C resulted in decomposition. After stirring at room temperature for 1 h a brief filtration of the reaction mixture through silica gel provided

Table 1. Reaction of *m*-phenylenediamine **6** and the iron complex salt **7**

Ratio, **6**:**7**	Reaction conditions	**8**, Yield (%)	**9**, Yield (%)
1:1	25°C, 18 h	39	30
1:1	60°C, 12 h	48	26
1:2	25°C, 18 h	19	71
1:2.2	25°C, 16 h	0	96



Scheme 2.



Scheme 3.

the new compound, which represents an intermediate tricarbonyliron complex as shown by IR spectroscopy. Moreover, the ^{1}H NMR spectrum of the crude product indicated a cyclization at one cyclohexadiene ring to a 4a,9a-dihydro-9*H*-carbazole. The feasibility to transform 4a,9a-dihydro-9*H*-carbazoles to aromatized 9*H*-carbazoles was already demonstrated in our previous studies.[17] Therefore, the intermediate iron complex was submitted to further oxidation with additional 3 equiv. of iodine in pyridine, which was carried out first at room temperature and then completed at 55°C to afford the indolo[2,3-*b*]carbazole **2** in 38% yield (Scheme 3).

The structural assignment for indolo[2,3-*b*]carbazole **2** is based on the spectroscopic data (see Experimental). Our melting point for compound **2** (348–350°C) is 10°C below the value reported by Grotta.[5] The IR, ^{1}H NMR, and mass spectra of indolo[2,3-*b*]carbazole **2** are in good agreement with those described by Grotta and Müllen.[5,6] The UV absorption spectrum of **2** was not reported previously. We found that indolo[2,3-*b*]carbazole **2** exhibits a typical carbazole UV spectrum,[18] but with some special features: the band at 303 nm has a notably strong extinction (ϵ=62 500) and there is an additional long-wavelength band at 360 nm with a molar extinction coefficient of ϵ=10 800. The ^{13}C NMR spectrum of compound **2** at 125 MHz in DMSO-d_6 is almost identical with the corresponding data published by Müllen[6] except for the signal of one of the methine carbons which appears at 90.66 ppm (instead of 107.38 ppm, as given in Ref. 6). Our assignment for the ^{13}C NMR signals of **2** is based on the ^{13}C NMR data reported for the parent 9*H*-carbazole,[19] and was additionally supported by the DEPT spectra and a ^{13}C,^{1}H correlated NMR spectrum of **2** (Fig. 2). The signal at 90.66 ppm was

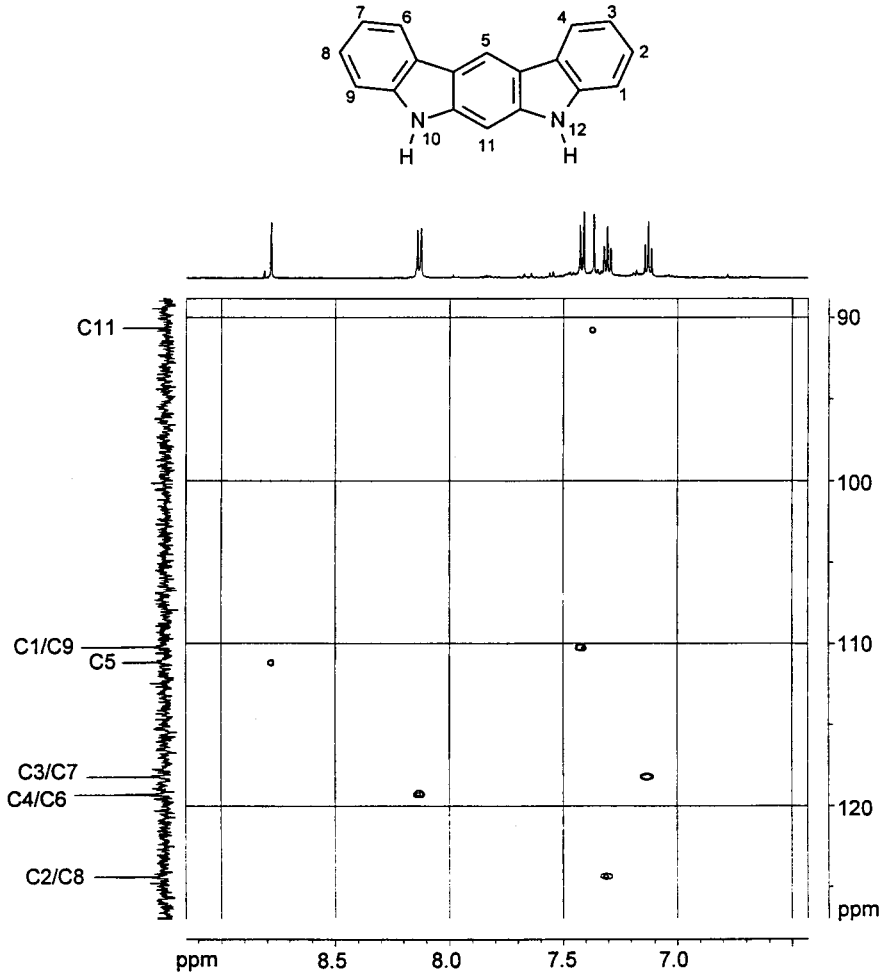


Figure 2. ^{13}C,^{1}H correlated NMR spectrum of **2** (125/500 MHz, DMSO-d_6).

assigned to C11. This characteristic high-field shift is obviously caused by the mesomeric effects of the two annulated indole rings with both nitrogen atoms in the *ortho* positions to C11.

In conclusion, we achieved a highly convergent synthesis of indolo[2,3-*b*]carbazole **2** by a double electrophilic aromatic substitution of *m*-phenylenediamine with the tricarbonyl(η^5-cyclohexadienyl)iron cation followed by double oxidative cyclization. The double iron-mediated consecutive C–C and C–N bond formation provides indolo[2,3-*b*]-carbazole in two steps and 36% overall yield based on commercial *m*-phenylenediamine. Moreover, we demonstrated that starting from a phenylenediamine two indole rings can be annulated simultaneously in a bidirectional synthesis, thus extending the scope of our iron-mediated synthesis of 9*H*-carbazoles.

Experimental

All reactions were carried out using anhydrous and degassed solvents under an inert gas atmosphere. Flash chromatography: Baker or Merck silica gel (0.03–0.06 mm). Melting points: Laboratory Devices (USA) MEL-TEMP II. UV: Perkin–Elmer Lambda 2 (UV/VIS spectrometer); λ in nm, ϵ in cm^2/mmol. IR: Bruker IFS-88 (FT-IR); $\tilde{\nu}$ in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra: Bruker DRX-500; internal standard: tetramethylsilane or the signal of the deuterated solvent; δ in ppm, coupling constants J in Hz. Mass spectra: Finnigan MAT-90, at an ionization potential of 70 eV. Elemental analysis: Heraeus CHN-Rapid.

[(1,4-η)-5-(2,4-Diaminophenyl)cyclohexa-1,3-diene]tricarbonyliron (8) and 1,5-diamino-2,4-bis{tricarbonyl[(2-5-η)-cyclohexa-2,4-dienyl]iron}benzene (9). A solution of the iron complex salt **7** (503 mg, 1.65 mmol) and *m*-phenylenediamine **6** (178 mg, 1.65 mmol) in acetonitrile (5 mL) was stirred for 18 h at room temperature. The solvent was evaporated in vacuo and the residue was subjected to flash chromatography (hexane/ethyl acetate/triethylamine, 5:10:2) on silica gel to afford **8** as the more polar fraction and **9** as the less polar fraction.

8. Colorless oil, yield: 207 mg (39%). IR (drift): $\tilde{\nu}$=3355, 3219, 3010, 2930, 2043, 1963, 1623, 1581, 1511, 1450, 1214, 842 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.57 (dt, J=15.2, 3.3 Hz, 1H), 2.33 (ddd, J=15.2, 11.1, 3.9 Hz, 1H), 3.14 (m, 1H), 3.16 (m, 1H), 3.30 (dt, J=11.1, 3.6 Hz, 1H), 3.47 (br s, 2H), 3.49 (br s, 2H), 5.48 (m, 2H), 5.97 (br s, 1H), 6.09 (br d, J=8.1 Hz, 1H), 6.88 (d, J=8.1 Hz, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=31.50 (CH_2), 38.24 (CH), 60.27 (CH), 65.44 (CH), 84.90 (CH), 85.64 (CH), 102.66 (CH), 106.34 (CH), 121.33 (C), 127.90 (CH), 144.39 (C), 145.54 (C), 212.10 (3 CO). MS (85°C): *m*/*z* (%)=326 (M$^+$, 25), 298 (2), 270 (53), 242 (30), 241 (16), 240 (100), 186 (18), 185 (24), 184 (66), 164 (93), 108 (31). HRMS: calcd for $C_{15}H_{14}FeN_2O_3$ (M$^+$): 326.0354, found: 326.0333.

9. Light brown crystals, yield: 273 mg (30%), 1:1 mixture of 2 diastereoisomers, mp 156–158°C (Ref. 11: mp 136–138°C). IR (drift): $\tilde{\nu}$=3433, 3368, 3224, 3003, 2927, 2859, 2041, 1962, 1628, 1577, 1511, 1431, 1263, 1155, 987, 860 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.59 (m, 2H), 2.32 (ddd, J=15.2, 11.0, 4.3 Hz) and 2.33 (ddd, J=15.2, 11.0, 4.2 Hz, Σ 2H), 3.13 (m, 2H), 3.20 (m, 2H), 3.28 (dt, J=11.0, 3.5 Hz, 2H), 3.41 (br s, 4H), 5.54 (m, 4H), 5.90 (s, 1H), 6.80 (s) and 6.82 (s, Σ 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=31.37 (CH_2), 31.41 (CH_2), 38.81 (CH), 38.84 (CH), 60.36 (CH), 60.39 (CH), 65.47 (CH), 65.57 (CH), 84.78 (CH), 84.84 (CH), 85.48 (CH), 85.52 (CH), 103.53 (CH), 121.46 (C), 121.50 (C), 126.44 (CH), 142.47 (2 C), 212.01 (6 CO). MS (130°C): *m*/*z* (%)=544 (M$^+$, 22), 488 (29), 460 (17), 458 (39), 400 (22), 372 (12), 344 (6), 324 (39), 316 (61), 296 (29), 260 (36), 240 (100), 184 (38), 164 (29), 108 (14). HRMS: calcd for $C_{24}H_{20}Fe_2N_2O_6$ (M$^+$): 544.0020, found: 544.0004. Anal. Calcd for $C_{24}H_{20}Fe_2N_2O_6$: C 52.97, H 3.70, N 5.15. Found: C 53.05, H 4.27, N 5.43.

1,5-Diamino-2,4-bis{tricarbonyl[(2-5-η)-cyclohexa-2,4-dienyl]iron}benzene (9). A solution of the iron complex salt **7** (554 mg, 1.81 mmol) and *m*-phenylenediamine **6** (89 mg, 0.82 mmol) in acetonitrile (5 mL) was stirred for 16 h at room temperature. Evaporation of the solvent and flash chromatography (hexane/ethyl acetate/triethylamine, 5:10:2) of the residue on silica gel afforded **9** as light brown crystals, yield: 431 mg (96%). Spectral data, see above.

Indolo[2,3-*b*]carbazole (2). Iodine (61 mg, 0.24 mmol) was added to a solution of the iron complex **9** (172 mg, 0.32 mmol) in pyridine (2 mL). After stirring for 1 h at room temperature additional iodine (183 mg, 0.72 mmol) was added and stirring was continued for 1 h. A brief filtration over a short path of silica gel (hexane/ether 2:1) provided an intermediate tricarbonyliron complex (161 mg). IR (drift): $\tilde{\nu}$=3466, 3373, 2043, 1966, 1616 cm^{-1}. This crude product was dissolved in pyridine (2 mL), iodine was added (first 56 mg, 0.22 mmol; and then additional 168 mg, 0.66 mmol), and the reaction mixture was stirred at room temperature for 18 h and at 55°C for 6 h. The solution was cooled and sodium dithionite (300 mg) was added. After stirring for 10 min the mixture was poured into 10% citric acid (50 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with water (2×25 mL) and dried over sodium sulfate. Removal of the solvent and flash chromatography (hexane/diethyl ether, 1:4) of the residue on silica gel afforded indolo[2,3-*b*]carbazole **2** as a colorless solid, yield: 31 mg (38%), mp 348–350°C (Ref. 5: mp 358-360°C). UV (EtOH): λ (ϵ)=209 (15600), 238 (28400), 265 (18900), 274 (19100), 303 (62500), 343 (7500), 351 (6500), 360 (10800) nm. IR (drift): $\tilde{\nu}$=3413, 3055, 2930, 1644, 1614, 1490, 1461, 1324, 1270, 1221, 827, 750, 729 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ=7.13 (t, J=7.6 Hz, 2H), 7.31 (t, J=7.6 Hz, 2H), 7.37 (s, 1H), 7.42 (d, J=7.6 Hz, 2H), 8.13 (d, J=7.6 Hz, 2H), 8.78 (s, 1H), 11.04 (s, 2H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ=90.66 (CH), 110.21 (2 CH), 111.15 (CH), 117.19 (2 C), 118.18 (2 CH), 119.26 (2 CH), 123.22 (2 C), 124.36 (2 CH), 140.18 (2 C), 140.30 (2 C). MS (170°C): *m*/*z* (%)=256 (M$^+$, 100), 255 (46), 128 (31). HRMS: calcd for $C_{18}H_{12}N_2$ (M$^+$): 256.1000, found: 256.0991.

Acknowledgements

This work was supported by the *Fonds der Chemischen Industrie* and the *Alexander von Humboldt-Stiftung* (post-doctoral fellowship to K. R. R.). We thank the *BASF AG*, Ludwigshafen, for a generous gift of pentacarbonyliron.

References

1. Part 60: Knölker, H.-J. *Chem. Rev.* **2000**, *100*, in print.
2. For reviews, see: Bhattacharyya, P.; Chakraborty, D. P. In *Prog. Chem. Org. Nat. Prod.*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Vol. 52; Springer: Wien, 1987; p 159; Pindur, U. *Chimia* **1990**, *44*, 406; Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967; Chakraborty, D. P.; Roy, S. In *Prog. Chem. Org. Nat. Prod.*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Vol. 57; Springer: Wien, 1991; p 71; Chakraborty, D. P. In *The Alkaloids*; Cordell, G. A., Ed.; Vol. 44; Academic Press: New York, 1993; p 257; Moody, C. J. *Synlett* **1994**, 681; Knölker, H.-J. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich (CT), 1995; Vol. 1, p 173.
3. Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *J. Chem. Soc. Chem. Commun.* **1978**, 800; Nettleton, D. E.; Doyle, T. W.; Krishnan, B.; Matsumoto, G. K.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4011; Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiot.* **1986**, *39*, 1059; Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535.
4. Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015; Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343; Lowinger, T. B.; Chu, J.; Spence, P. L. *Tetrahedron Lett.* **1995**, *36*, 8383; Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825; Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641; Wood, J. L.; Stoltz, B. M.; Goodman, S. N.; Onwueme, K. *J. Am. Chem. Soc.* **1997**, *119*, 9652; Kobayashi, Y.; Fujimoto, T.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 6501.
5. Grotta, H. M.; Riggle, C. J.; Bearse, A. E. *J. Org. Chem.* **1961**, *26*, 1509.
6. Kistenmacher, A.; Müllen, K. *J. Heterocycl. Chem.* **1992**, *29*, 1237.
7. Tomlinson, M. *J. Chem. Soc.* **1951**, 809; Mann, F. G.; Willcox, T. J. *J. Chem. Soc.* **1958**, 1525; Robinson, B. *J. Chem. Soc.* **1963**, 3097; Hünig, S.; Steinmetzer, H.-C. *Liebigs Ann. Chem.* **1976**, 1090; Desarbre, E.; Bergman, J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2009; Janosik, T.; Bergman, J. *Tetrahedron* **1999**, *55*, 2371.
8. For a preliminary communication, see: Knölker, H.-J.; Reddy, K. R. *Tetrahedron Lett.* **1998**, *39*, 4007.
9. For reviews, see: Knölker, H.-J. In *Organic Synthesis via Organometallics*; Dötz, K. H., Hoffmann, R. W., Eds.; Vieweg: Braunschweig, 1991; p 119; Knölker, H.-J. *Synlett* **1992**, 371; Knölker, H.-J. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Vol. 1; Wiley-VCH: Weinheim, 1998; Chapter 3.13, p 534; Knölker, H.-J. *Chem. Soc. Rev.* **1999**, *28*, 151.
10. For more recent applications, see: Knölker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron* **1999**, *55*, 10391; Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett.* **1999**, *40*, 6915; Knölker, H.-J.; Baum, E.; Reddy, K. R. *Tetrahedron Lett.* **2000**, *41*, 1171; Knölker, H.-J.; Baum, E.; Reddy, K. R. *Chirality* **2000**, *12*, 526.
11. Birch, A. J.; Liepa, A. J.; Stephenson, G. R. *Tetrahedron Lett.* **1979**, 3565; Birch, A. J.; Liepa, A. J.; Stephenson, G. R. *J. Chem. Soc. Perkin Trans. 1* **1982**, 713.
12. Manganese dioxide (precipitated active) from Merck–Schuchardt (art. 805958).
13. Pearson, A. J.; Ong, C. W. *J. Org. Chem.* **1982**, *47*, 3780.
14. Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B. *Chem. Ber.* **1992**, *125*, 2783.
15. Knölker, H.-J.; Bauermeister, M. *J. Indian Chem. Soc.* **1994**, *71*, 345.
16. Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett.* **1996**, *37*, 9183.
17. Knölker, H.-J.; Baum, G.; Pannek, J.-B. *Tetrahedron* **1996**, *52*, 7345.
18. Chakraborty, D. P.; Dutta, J.; Ghosh, A. *Sci. Cult.* **1965**, *31*, 529.
19. Kalinowski, H.-O.; Berger, S.; Braun, S. *^{13}C NMR-Spektroskopie*; Thieme-Verlag: Stuttgart, 1984; p 359.