Transition Metal-Catalyzed Annulation Reactions, VII[1]

Palladium-Catalyzed C–H Activation at Methoxy Groups: Regiochemistry of the Domino Coupling Process

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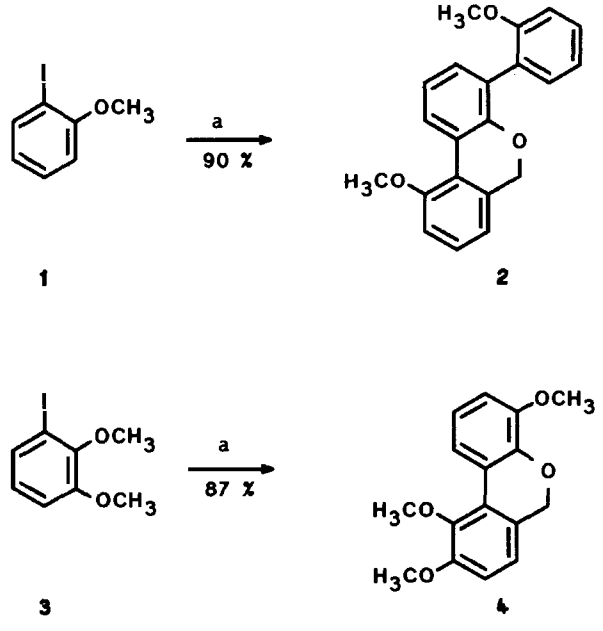
By palladium catalysis substituted *ortho*-iodoanisoles (**5**, **8**, **10**, **13**) are transformed either to annulated pyran (**6**) or furan derivatives (**7**, **9**, **11**, **14**, **15**), depending on the reactivity of additional substituents. The regiochemistry of the domino coupling processes is analyzed and a mechanistic rationale developed. Key step is the C–H activation at methoxy groups.

For the activation of relatively unreactive carbon-hydrogen bonds metalation reactions are very often the method of choice. Especially interesting for this purpose is the application of transition metals to achieve a catalytic realization. The activation of olefinic[2], acetylenic[3], and even of aromatic[4] C–H bonds by palladium catalysts is already well established and has proven to be a valuable key step in coupling reactions with vinyl and aryl halides: by dehydrohalogenation C–C bonds are formed giving rise to a multitude of applications in organic synthesis. In contrast only little information is available on the catalytic C–H activation at saturated alkyl and heteroalkyl groups. Such reactions should open up new synthetic pathways. Recently, we reported on the first palladium-catalyzed C–H activation at a methoxy group: 2-iodoanisole (**1**) reacts in a threefold homocoupling process to give a 90% yield of the substituted dibenzopyran **2**[5]. In the case of 1-iodo-2,3-dimethoxybenzene (**3**) the condensation product **4** is obtained, which originates from only two equivalents of the starting compound **3**. Obviously, the additional methoxy group in the 3-position is blocking a third condensation step. We have now tested a series of 3-substituted 1-iodo-2-methoxybenzenes in palladium-catalyzed homocoupling reactions to study the influence of these additional substituents on the regiochemical course of the domino coupling process.



a: 4 mol-% $Pd(OAc)_2$, K_2CO_3, n-Bu_4NBr, DMF, 100 °C.

Results and Discussion

In analogy to the coupling reaction of **3** the anisole derivative **5** is converted into a substituted dibenzopyran **6** as the main product in 47% yield. Surprisingly, as a byproduct a 2,3-dihydrobenzofuran **7** is isolated in 31% yield. Clearly, the methyl group in the 3-position opens up a new reaction pathway and directly takes part in the domino coupling process. In the case of the substituted *ortho*-iodoanisole **8** the additional second methyl group should prevent the formation of a dibenzo[*b*,*d*]pyran system by blocking a crucial position. Indeed, the benzofuran **9** now becomes the main product with 25% yield (45% based on recovered starting material; the reaction is quite sluggish presumably because of steric and electronic reasons). With the benzo-annulated starting material **10** the naphthofuran **11** is accessible in good yield; the competing formation of the dinaphthopyran **12** has not been observed. Similarly, no pyran derivative is formed by the coupling reaction of the functionalized stilbene **13**. In this case the aromatized benzofuran **14** is isolated as the main product; the spectroscopic data of the

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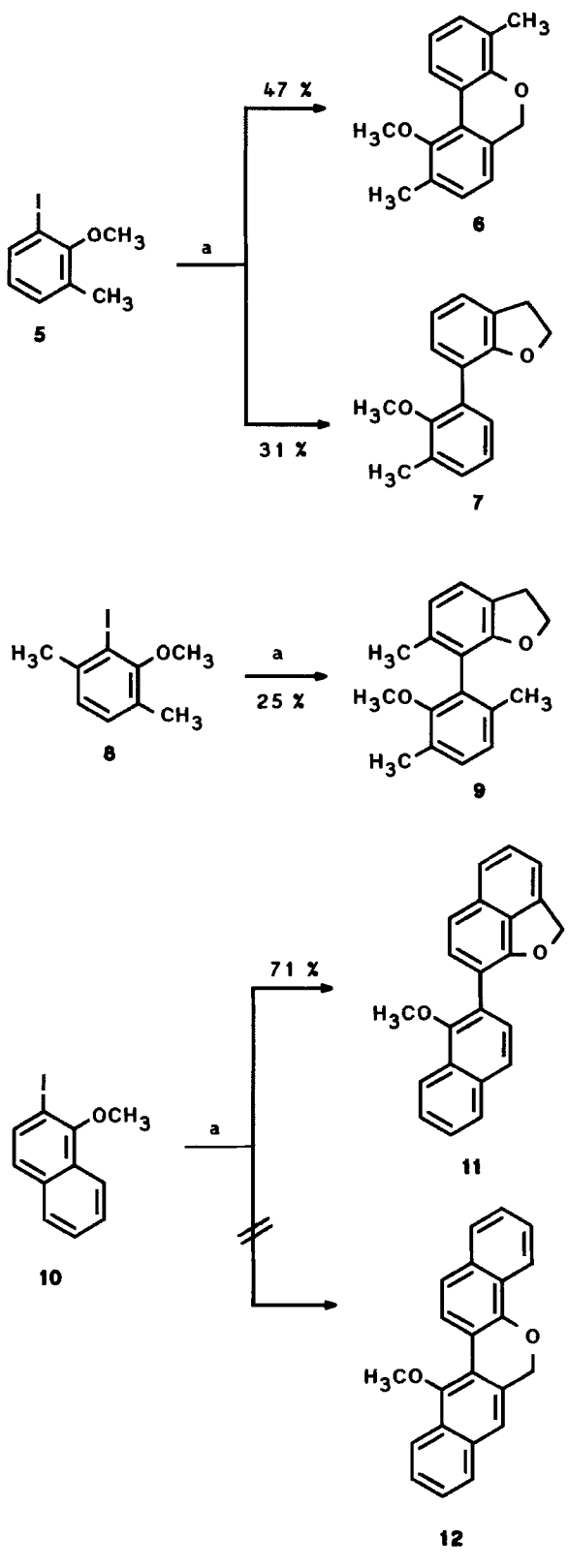
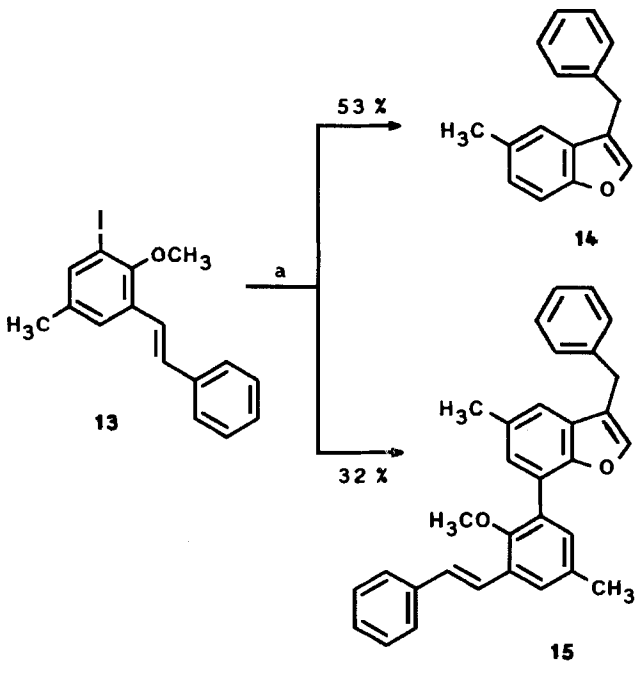


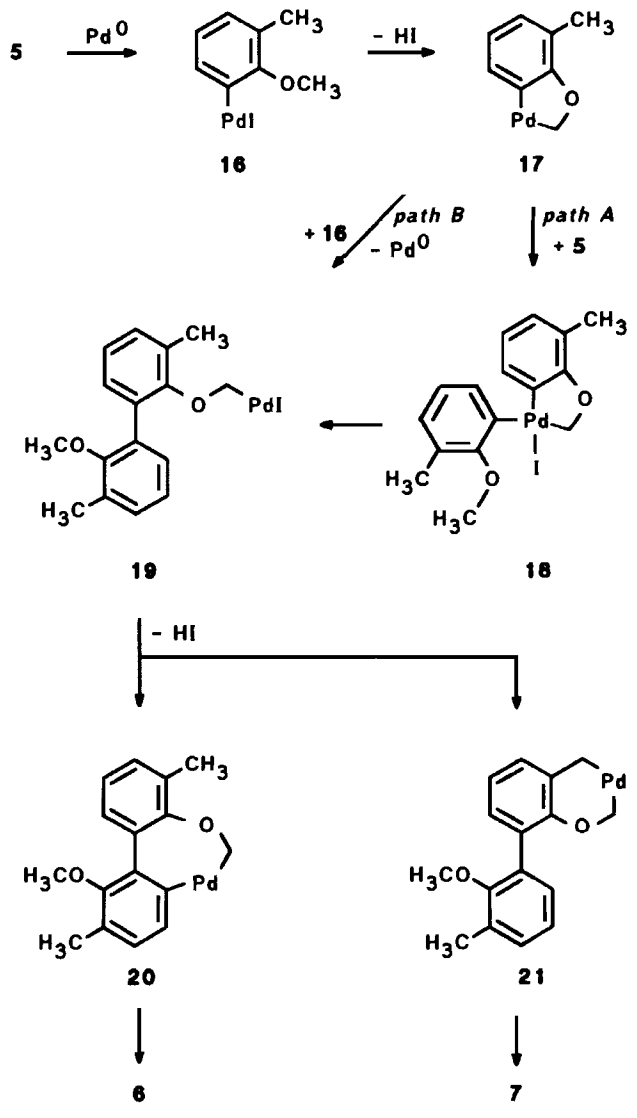
a: 4 mol-% $Pd(OAc)_2$, K_2CO_3, $n\text{-}Bu_4NBr$, DMF, 100 °C



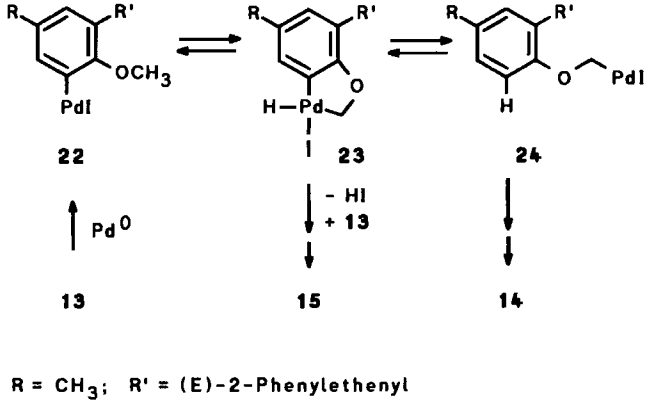
a: 4 mol-% $Pd(OAc)_2$, K_2CO_3, $n\text{-}Bu_4NBr$, DMF, 100 °C

byproduct – including a $^1H,^1H$-COSY and a $^1H,^{13}C$-COSY spectrum – is consistent with structure **15**.

Considering the diversity of the observed products, we have developed a mechanistic rationale for the regiochemistry of the studied domino coupling process. By using the condensation reaction of **5** as an example, we propose a mechanism that is in accord with all experimental findings. Oxidative addition of a Pd^0 species to **5** should lead to a arylpalladium(II) iodide complex **16** in the first step (additional ligands – presumably DMF – have been omitted for clarity). The decisive reaction step is suggested to be the cyclometalation to the five-membered ring compound **17** involving an intramolecular C–H activation at the neighboring methoxy group. Oxidative addition of the second equivalent of **5** and subsequent reductive elimination with C–C bond formation via the Pd^{IV} intermediate[6] **18** (path A) should build up the biarene species **19**. A mechanistic alternative for the biarene bond forming process are ligand exchange reactions[7] between the Pd^{II}-centered complexes **16** and **17** (path B), avoiding Pd^{IV} intermediates but requiring two palladium atoms for the catalytic cycle. In the final ring closure formation of the dibenzopyran **6** presumably via the seven-membered palladacycle **20** is competing with the unusual metalation at the neighboring methyl group giving rise to the six-membered palladacycle **21** and ultimately leading to the benzofuran system **7**. According to the product ratio the latter pathway is slightly disfavored. In the case of the homocoupling reactions of **10** and **13** we have observed the opposite regioselectivity. In contrast to **5** these substrates offer sp^2-centered neighboring groups for the final cyclometalation leading to benzofurans. In conclusion, the final ring closure at an sp^2-centered C–H bond to give a pyran ring is strongly disfavored in comparison with the furan ring formation at an sp^2 center, but slightly favored compared with furan ring formation at an sp^3 center.



To explain the formation of benzofuran **14** the introduced mechanistic scheme has to be complemented with respect to the decisive C–H activation step at the methoxy group. Since the absence of stronger ligands like triphenylphosphane is necessary for the C–H activation to occur, complexation of the coordinatively unsaturated palladium atom in **22** by the neighboring methoxy group might lead to intermediate **23** by oxidative addition[8]. The hetero atom does not seem to be involved in this process, because *tert*-butyl groups behave similarly[9]. Dehydrogenation of Pd^{IV} complex **23** represents the usual pathway already discussed above and finally leads to product **15**. However, reductive elimination to **24** initiates the terminating ring closure to **14**, in this case an especially favored process because of the reactive neighboring alkene.



R = CH_3; R' = (E)-2-Phenylethenyl

To summarize, the palladium-catalyzed C–H activation at methoxy groups of substituted *ortho*-iodoanisoles opens up new reaction pathways to a variety of interesting products. Additional substituents enable the regiochemistry of the domino coupling process to be analyzed either in the sense of inert markers or as participating groups. The mechanistic rationale developed takes into account unusual catalytic Pd^{II}-Pd^{IV} cycles in addition to the well established Pd^0-Pd^{II} cycles.

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Experimental

Melting point determinations are uncorrected. – ^1H NMR: Bruker AM 400 spectrometer, 400.1 MHz, $CDCl_3$ as solvent, TMS as internal standard. – ^{13}C NMR: Bruker AM 400 spectrometer, 100.6 MHz, $CDCl_3$ as solvent and as internal standard (δ = 77.05). – High- and low-resolution MS: 70 eV, electron impact. – The *ortho*-iodomethoxyarenes **5**, **8**, and **10** were synthesized by iodolysis of the corresponding aryllithium compounds[10], and **13** was prepared by Heck reaction[2] of 2,6-diiodo-4-methylanisole[11] with styrene in analogy to published methods.

General Procedure for the Homocoupling Reaction of ortho-Iodomethoxyarenes: A mixture of 2.0 mmol of *ortho*-iodomethoxyarene, 1.1 g (8.0 mmol) of potassium carbonate, 645 mg (2.00 mmol) of tetra-*n*-butylammonium bromide, 12 mg (53 μmol) of palladium acetate, and 10 ml of DMF in a sealed tube (for convenience) was stirred under N_2 at 100°C for 3–7 d. After dilution with water (50 ml) the reaction mixture was extracted three times with ether (50 ml). The combined ether extracts were filtered through silica gel and the solvent was removed by evaporation. The crude product was purified by flash chromatography (silica gel, hexanes or diethyl ether/hexanes, 1:20).

10-Methoxy-4,9-dimethyl-6H-dibenzo[b,d]pyran (**6**) *and 2,3-Dihydro-7-(2-methoxy-3-methylphenyl)benzofuran* (**7**): From 496 mg (2.00 mmol) of **5**; reaction time 4 d. – 1st fraction with R_f = 0.40 (silica gel, hexanes): 112 mg (47%) of **6** as a colorless solid with m.p. 70–72°C after kugelrohr distillation (150°C/0.1 Torr). – IR (KBr): $\tilde{\nu}$ = 2951 cm^{-1} (m), 2927 (m), 1456 (s), 1394 (s), 1252 (s), 1052 (s), 809 (s). – UV (acetonitrile): λ_{max} (lg ε) = 216 nm (4.576), 240 (sh, 3.982), 268 (4.105), 276 (4.124), 300 (3.774). – ^1H NMR ($CDCl_3$): δ = 2.28 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 4.96 (s, 2H, 6-H), 6.86 (d, J = 7.5 Hz, 1H), 6.97 ("t", "J" = 7.7 Hz, 1H, 2-H), 7.10 (d, br, "J" = 7.6 Hz, 2H), 8.28 (m_d, "J" = 8.2 Hz, 1H, 1-H). – ^{13}C NMR ($CDCl_3$): δ = 16.16 (q), 16.28 (q), 59.25 (q), 68.75 (t), 120.19 (d), 121.52 (d), 121.63 (s), 123.01 (s), 125.39 (d), 126.38 (s), 130.09 (d), 130.41 (d), 132.02 (s), 133.04 (s), 153.61 (s), 155.71 (s). – MS, *m/z* (%): 241 (17), 240 (100) [M^+], 239 (51), 225 (50), 209 (47), 195 (22), 165 (20). – $C_{16}H_{16}O_2$ (240.3): calcd. C 79.97, H 6.71; found C 79.74, H 6.69.

2nd Fraction with R_f = 0.06 (silica gel, hexanes): 74 mg (31%) of **7** as colorless crystals with m.p. 117–118°C (from pentane). –

IR (KBr): $\tilde{\nu}$ = 2925 cm^{-1} (m), 1464 (s), 1447 (s), 1226 (s), 1205 (s), 1013 (s), 773 (s). – UV (acetonitrile): λ_{max} (lg ε) = 206 nm (4.596), 244 (3.856), 290 (3.697). – ^{1}H NMR ($CDCl_3$): δ = 2.34 (s, 3H, CH_3), 3.27 (t, *J* = 8.7 Hz, 2H, 3-H), 3.44 (s, 3H, OCH_3), 4.57 (t, *J* = 8.7 Hz, 2H, 2-H), 6.90 ("t", "*J*" = 7.5 Hz, 1H), 7.05 ("t", "*J*" = 7.5 Hz, 1H), 7.15–7.23 (m, 4H). – ^{13}C NMR ($CDCl_3$): δ = 16.40 (q), 30.03 (t), 60.16 (q), 71.09 (t), 120.23 (d), 121.63 (s), 123.61 (d), 123.96 (d), 127.12 (s), 129.26 (d), 129.51 (d), 130.55 (s), 130.64 (d), 131.38 (s), 156.30 (s), 157.46 (s). – MS, *m/z* (%): 241 (19), 240 (100) [M^+], 225 (37), 210 (11). – $C_{16}H_{16}O_2$ (240.3): calcd. C 79.97, H 6.71; found C 80.05, H 6.79.

2,3-Dihydro-7-(2-methoxy-3,6-dimethylphenyl)-6-methylbenzofuran (**9**): From 524 mg (2.00 mmol) of **8**; reaction time 7 d. – 1st fraction with R_f = 0.6 (silica gel, diethyl ether/hexanes, 1:20): 232 mg (44%) of recovered starting material **8**. – 2nd fraction with R_f = 0.2 (silica, diethyl ether/hexanes, 1:20): 68 mg (25%) of **9** as a colorless solid with m.p. 62°C after kugelrohr distillation (200°C/0.1 Torr). – IR (KBr): $\tilde{\nu}$ = 2926 cm^{-1} (m), 1589 (w), 1456 (s), 1249 (s), 1240 (s), 1062 (s), 957 (m), 809 (m). – UV (acetonitrile): λ_{max} (lg ε) = 202 nm (4.739), 288 (3.578). – ^{1}H NMR ($CDCl_3$)[12]: δ = 1.97 (s, 3H, 6′-CH_3), 1.99 (s, 3H, 6-CH_3), 2.28 (s, 3H, 3′-CH_3), 3.21 (t, br, "*J*" = 8.7 Hz, 2H, 3-H), 3.41 (s, 3H, OCH_3), 4.49 (m_t, "*J*" = 8.7 Hz, 2H, 2-H), 6.79 (d, *J* = 7.4 Hz, 1H, 5-H), 6.96 (d, *J* = 7.6 Hz, 1H, 5′-H), 7.08 (d, *J* = 7.6 Hz, 1H, 4′-H), 7.09 (d, *J* = 7.4 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 16.09 (q, 3′-CH_3), 19.39 (q, 6′-CH_3), 19.43 (q, 6-CH_3), 29.97 (t, C-3), 59.89 (q, OCH_3), 71.36 (t, C-2), 119.85 (s, C-7), 121.72 (d, C-5), 123.36 (d, C-4), 123.71 (s, C-3a), 125.29 (d, C-5′), 128.15 (s, C-3′), 129.64 (s, C-1′), 130.30 (d, C-4′), 135.90 (s, C-6′), 136.63 (s, C-6), 156.21 (s, C-2′), 157.81 (s, C-7a). – MS, *m/z* (%): 269 (20), 268 (100) [M^+], 253 (58), 238 (39), 237 (28), 223 (19), 178 (26), 165 (43), 152 (25). – $C_{18}H_{20}O_2$ (268.35): calcd. C 80.56, H 7.51; found C 80.55, H 7.53.

8-(1-Methoxy-2-naphthyl)-2H-naphtho[1,8-bc]furan (**11**): From 568 mg (2.00 mmol) of **10**; reaction time 3 d. Yield: 222 mg (71%) of **11** as colorless needles with m.p. 138°C (from diethyl ether/pentane). – IR (KBr): $\tilde{\nu}$ = 2932 cm^{-1} (w), 1616 (w), 1564 (w), 1364 (s), 1332 (s), 1105 (s), 987 (s), 920 (s), 809 (s), 750 (s). – UV (acetonitrile): λ_{max} (lg ε) = 216 nm (4.373), 244 (sh, 4.270), 262 (4.479), 332 (3.777). – ^{1}H NMR ($CDCl_3$)[12]: δ = 3.63 (s, 3H, OCH_3), 5.85 (s, 2H, 2-H), 7.25 (m_d, "*J*" = 6.8 Hz, 1H, 3-H), 7.35 (d, *J* = 8.4 Hz, 1H, 6-H), 7.47–7.54 (m, 3H, 4-, 6′-, 7′-H), 7.67 ("d", "*J*" = 8.1 Hz, 1H, 5-H), 7.68 (d, *J* = 8.6 Hz, 1H, 4′-H), 7.73 (d, *J* = 8.6 Hz, 1H, 3′-H), 7.77 (d, *J* = 8.4 Hz, 1H, 7-H), 7.85 (m_d, "*J*" = 7.6 Hz, 1H, 5′-H), 8.27 (m_d, "*J*" = 7.9 Hz, 1H, 8′-H). – ^{13}C NMR ($CDCl_3$): δ = 61.34 (q, OCH_3), 77.35 (t, C-2), 112.59 (s, C-8), 115.53 (d, C-3), 115.83 (d, C-6), 122.53 (d, C-8′), 122.88 (d, C-5), 123.70 (d, C-4′), 124.96 (s, C-2′), 126.00 (d, C-7′), 126.20 (d, C-6′), 127.80 (d, C-5′), 128.62 (d, C-4), 128.68 (s, C-8a′), 128.98 (d, C-3′), 128.98 (s, C-8b), 131.34 (s, C-5a), 132.05 (d, C-7), 134.41 (s, C-4a′), 139.08 (s, C-2a), 153.64 (s, C-1′), 158.88 (s, C-8a). – MS, *m/z* (%): 313 (25), 312 (100) [M^+], 298 (19), 297 (80), 281 (24), 269 (20), 239 (19). – $C_{22}H_{16}O_2$ (312.4): calcd. C 84.59, H 5.16; found C 84.53, H 5.10.

3-Benzyl-5-methylbenzofuran (**14**) *and 3-Benzyl-7-{2-methoxy-5-methyl-3-[(E)-2-phenylethenyl]phenyl}-5-methylbenzofuran* (**15**): From 700 mg (2.00 mmol) of **13**; reaction time 4 d. – 1st fraction with R_f = 0.25 (silica gel, diethyl ether/hexanes, 1:20): 235 mg (53%) of **14** as colorless crystals with m.p. 83–84°C. – IR (KBr): $\tilde{\nu}$ = 2916 cm^{-1} (w), 1494 (m), 1476 (m), 1453 (m), 1434 (m), 1180 (m), 1083 (s), 804 (m), 788 (m), 747 (m), 702 (s). – UV (acetonitrile): λ_{max} (lg ε) = 210 nm (4.525), 252 (3.962), 282 (3.434), 290 (3.501). – ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 7.08 (m_d, "*J*" = 8.3 Hz, 1H), 7.19–7.35 (m, 8H). – ^{13}C NMR ($CDCl_3$): δ = 21.37 (q), 29.96 (t), 110.97 (d), 119.40 (s), 119.65 (d), 125.52 (d), 126.35 (d), 128.12 (s), 128.53 (d), 128.64 (d), 131.83 (s), 139.33 (s), 142.36 (d, C-2), 154.00 (s). – MS; *m/z* (%): 223 (20), 222 (100) [M^+], 207 (13), 178 (23), 145 (34), 115 (18). – $C_{16}H_{14}O$ (222.3): calcd. C 86.45, H 6.35; found C 86.55, H 6.37.

2nd fraction with R_f = 0.03 (silica gel, diethyl ether/hexanes, 1:20): 142 mg (32%) of **15** as colorless solid with m.p. 60–64°C (from 2-propanol/methanol, 1:1, at −20°C). – IR (KBr): $\tilde{\nu}$ = 3027 cm^{-1} (m), 2921 (m), 1600 (m), 1494 (s), 1465 (s), 1228 (s), 1098 (s), 1009 (s), 748 (s), 709 (s), 694 (s). – UV (acetonitrile): λ_{max} (lg ε) = 218 nm (sh, 4.576), 294 (4.420), 314 (sh, 4.331). – ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.39 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2), 7.16 (d, *J* = 16.5 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.20–7.32 (m, 8H), 7.35 (m_t, "*J*" = 7.2 Hz, 2H), 7.36 (s, br, 1H, 2-H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.51 (d, *J* = 16.5 Hz, 1H), 7.55 (m_d, "*J*" = 7.3 Hz, 2H). – ^{13}C NMR ($CDCl_3$): δ = 21.02 (q), 21.41 (q), 30.09 (t), 61.57 (q), 118.98 (d), 119.40 (s), 122.33 (s), 123.53 (d), 126.36 (d), 126.57 (d), 126.63 (d), 126.86 (d), 127.58 (d), 128.35 (s), 128.54 (d), 128.69 (d, br), 129.65 (d), 130.30 (s), 130.82 (s), 131.77 (d), 131.92 (s), 133.45 (s), 137.81 (s), 139.33 (s), 142.58 (d), 151.63 (s), 153.84 (s). – MS, *m/z* (%): 445 (34), 444 (100) [M^+], 429 (9), 91 (19). – $C_{32}H_{28}O_2$ (444.6): calcd.C 86.45, H 6.35; found C 86.43, H 6.28.

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[12] The NMR signals of **9** and **11** were assigned by means of 2D NMR spectra (H,H COSY, C,H COSY, and COLOC).

[361/93]