Synthesis of 3,5-Disubstituted 4-Hydroxybenzoates by Aryl−Aryl and Alkynyl−Aryl Coupling

Adelheid Godt,* Ömer Ünsal, and Mark Roos

Max-Planck-Institut für Polymerforschung, Ackermannweg 10, D-55128 Mainz, Germany

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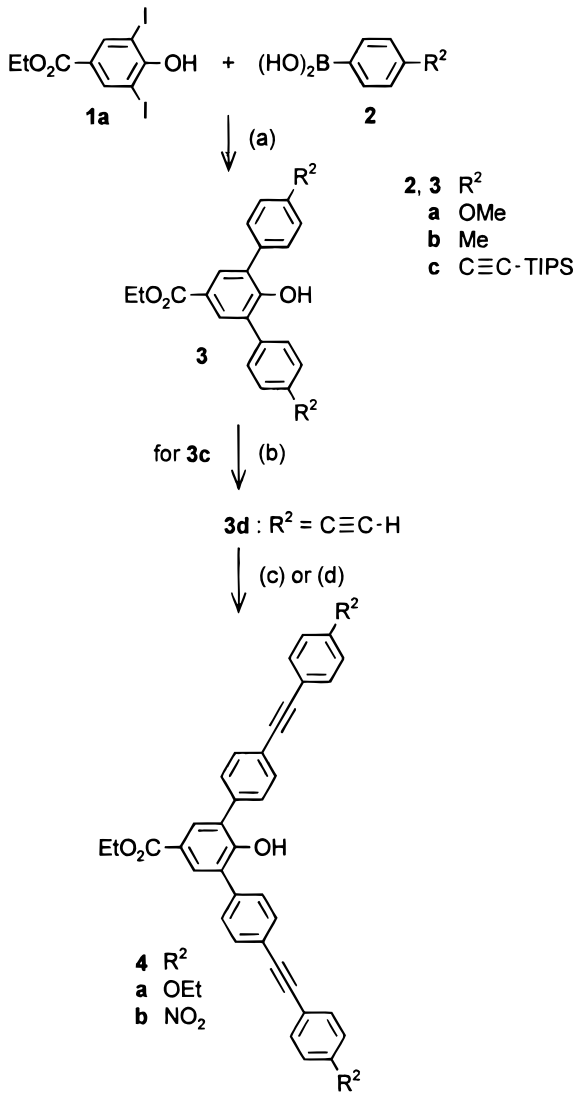
Angled molecules such as 1,3-diarylbenzene,[1] 1,3-di(arylethynyl)benzene,[2] and 1,3-di(arylbutadiynyl)benzene[3] have been used as building blocks for macrocycles and polymers. Frequently, these building blocks carry functional groups either in the 2- or 5-position and are, therefore, interesting ligands for transition metals[4] or key building blocks for functionalized nanoscopic objects.[1−3] 1,3-Diarylbenzene, 1,3-di(arylethynyl)benzene, and 1,3-di(arylbutadiynyl)benzene with a functional group in the 2-position and additionally a second, selectively addressable, functional group in the 5-position are rare,[3,5] though even more versatile building blocks for the above-mentioned applications. We were interested in a general approach to such compounds with functional groups that can be easily derivatized. The latter requirement will allow for a fine-tuning of the final functional groups at a late step in the synthesis. As the target structures, we choose 4-hydroxybenzoate with aryl-, arylethynyl-, and arylbutadiynyl substituents in the 3- and 5-positions. Here, we report on the synthesis of the angled compounds **3**, **4**, **8**, and **12** by aryl−aryl[6] or aryl−alkynyl[7] coupling starting from readily available ethyl 3,5-diiodo-4-hydroxybenzoate (**1a**).[8]

Results and Discussion

Ethyl 3,5-Diaryl-4-hydroxybenzoates 3 and 4 (Scheme 1). The terphenylenes **3a**,**b** were obtained by Suzuki coupling[6] of diiodo hydroxybenzoate **1a** with aryl boronic acids **2a**,**b**, catalyzed by $Pd_2(dba)_3$ in acetone/water with potassium carbonate as the base.[9] Careful degassing of the reaction mixture was essential to give a very high conversion of **1a**.[10]

Scheme 1[a]



[a] Key: (a) $Pd_2(dba)_3$, K_2CO_3 (for **3a**,**b**) or Cs_2CO_3 (for **3c**), acetone, water, reflux (**3a**: 70%; **3b**: 88%; **3c**: 81%); (b) *n*-Bu_4NF, THF, rt (**3d**: 99%); (c) 1-ethoxy-4-iodobenzene, $Pd(PPh_3)_2Cl_2$, CuI, piperidine, rt (**4a**: 81%); (d) 1-iodo-4-nitrobenzene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, rt (**4b**: 80%).

The same approach should be suitable for the preparation of larger building blocks such as **4** with the corresponding boronic acids as coupling partners. Alternatively, one can prepare a terphenylene unit with funtional groups at the phenyl substituents which allows, in a second step, for the enlargement of these phenyl substituents. The latter strategy was realized by the coupling of boronic acid **2c** with diiodo hydroxybenzoate **1a** to give

* To whom correspondence should be addressed. E-mail: godt@mpip-mainz.mpg.de.

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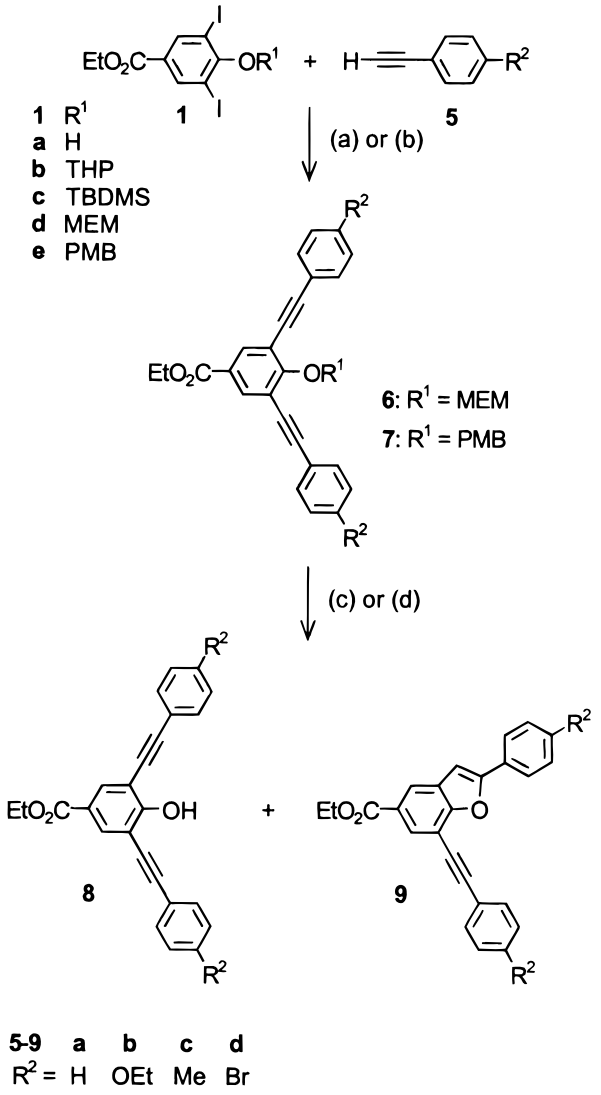
the terphenylene **3c**. Desilylation of **3c** with *n*-Bu_4NF gave **3d**, which coupled cleanly and quantitatively with iodobenzene derivatives giving the extended, angular molecules **4**. Whereas the terphenylenes **3a**,**b** were obtained in satisfying yields (70−88%), the yield of **3c** was rather low (50%) when prepared under the same conditions. Replacing potassium carbonate with cesium carbonate increased the yield of **3c** significantly (81%).[11] The boronic acid **2c** was prepared in two steps: (1) coupling of 1-bromo-4-iodobenzene with triisopropylsilylethyne (85%) and (2) halogen metal exchange and workup with triisopropyl borate (90%).[12] The boronic acid **2c** can be prepared easily in multigram amounts and is therefore a convenient building block for a sequence of coupling reactions involving first the boronic acid and then the alkyne functionality as demonstrated by the synthesis of compounds **4** via **3c**.

Ethyl 3,5-Di(2-arylethynyl)-4-hydroxybenzoates 8 (Scheme 2). In contrast to the coupling of **1a** with arylboronic acids, a direct coupling of **1a** with phenylethyne (**5a**) in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in piperidine[7] at room temperature did not give **8a** but, in addition to some starting material, the benzofuran **9a**.[13] A similar reaction, the Pd/Cu-catalyzed reaction of 2,4,6-triiodophenol with phenylethyne in triethylamine, has been reported to give the nonisomerized coupling product in good yield.[14] However, the formation of benzofuran during such coupling reactions has also been described.[15]

Consequently, the OH group was protected prior to the aryl−alkynyl coupling step. Attempts to synthesize the THP-ether **1b** failed.[16] The TBDMS ether **1c**,[17] MEM-ether **1d**, and *p*-methoxybenzyl (PMB) ether **1e**[18] were easily prepared. These compounds showed a varying suitability for alkynyl−aryl coupling. The coupling of TBDMS ether **1c** with *p*-tolylethyne (**5c**) in piperidine or triethylamine/THF in the presence of $Pd(PPh_3)_2Cl_2$ and CuI gave product mixtures consisting mainly of benzofuran **9c** or containing significant amounts of benzofuran **9c**, respectively. Coupling of MEM-ether **1d** with arylethynes **5c**,**d** resulted in formation of **6c**,**d** accompanied by ca. 10% or more of benzofurans **9c**,**d**. The formation of benzofuran was easily understood after discovering that the MEM group of **1d** is cleaved in piperidine at room temperature. The best results were obtained using the PMB-ether **1e**. The coupling reaction of **1e** with **5b**−**d** in piperidine in the presence of $Pd(PPh_3)_2Cl_2$ and CuI proceeded fast and quantitatively to give the products **7b**−**d** accompanied by small, varying amounts of corresponding benzofurans **9b**−**d** (0−6%; determined by ^1H NMR spectroscopy[19]). The formation of benzofurans indicated that even the PMB-group is labile under the reaction conditions. Indeed, we found that the PMB-group is cleaved off slowly when **1e** (quantitative cleavage after a maximum of 15 h) or the coupling products **7b**,**c** (60−80% cleavage after 22.5 h) are heated to 60 °C in piperidine. This suggested that control of temperature and reaction time during the slightly exothermic coupling reaction is important in order to minimize the extent of benzofuran formation. Using a base with a lower nucleophilicity than that of piperidine may also avoid deprotection and consequently benzofuran formation. To test this hypothesis, a mixture of triethylamine and THF was used instead of piperidine as the base and solvent for the coupling reaction of **1e** with **5c**,**d**. A quantitative and

Scheme 2[a]



[a] Key: (a) $Pd(PPh_3)_2Cl_2$, CuI, piperidine, rt (**7b**: 54%); (b) $Pd(PPh_3)_2Cl_2$, CuI, THF, Et_3N, rt (**7c**: 80%; **7d**: 78%); (c) concd HCl, EtOH, CH_2Cl_2, reflux (**8d**: 92%); (d) TMSCl, $SnCl_2$, anisole, CH_2Cl_2, rt (**8c**: 62%; **8d**: 63%). THP = tetrahydropyran-2-yl; TBDMS = *tert*.butyl-dimethylsilyl; MEM = methoxyethoxymethyl; PMB = 4-methoxybenzyl.

(11) Cs_2CO_3 as the base in Suzuki coupling reactions has been used occasionally: Littke, A. F.; Fu, G. C. *Angew. Chem.* **1998**, *110*, 3586; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387 and literature therein.

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(13) Benzofurans **9** and **13** have not been isolated from these experiments. They have been prepared separately from phenols **8** or **12** (Godt, A. Manuscript in preparation). With the help of the known NMR data of benzofurans **9** and **13**, the side product of the deprotection step could be easily identified as the benzofuran. Characteristic signals are the doublets of the two protons in ortho position to the ester group above 8 ppm and the singlet at ca. 7.0 ppm caused by the proton at the furan ring. Representatively, the analytical data of **9c** and **13c** are given in the Supporting Information.

(14) Tao, W.; Nesbitt, S.; Heck, R. F. *J. Org. Chem.* **1990**, *55*, 63.

(15) E. g.: (a) Arcadi, A.; Marinelli, F.; Cacchi, S. *Synthesis* **1986**, 749. (b) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *2815*.

(16) 3,4-Dihydro-2*H*-pyran, TsOH monohydrate or pyridinium tosylate, diethyl ether, rt or 0 °C.

(17) Preparation according to Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(18) Godt, A. *J. Org. Chem.* **1997**, *62*, 7471.

(19) Very small amounts of benzofuran **9** were estimated with the help of the ^{13}C satellites of the singlet corresponding to the protons of the 4-hydroxybenzoate unit of compounds **7** or **8**.

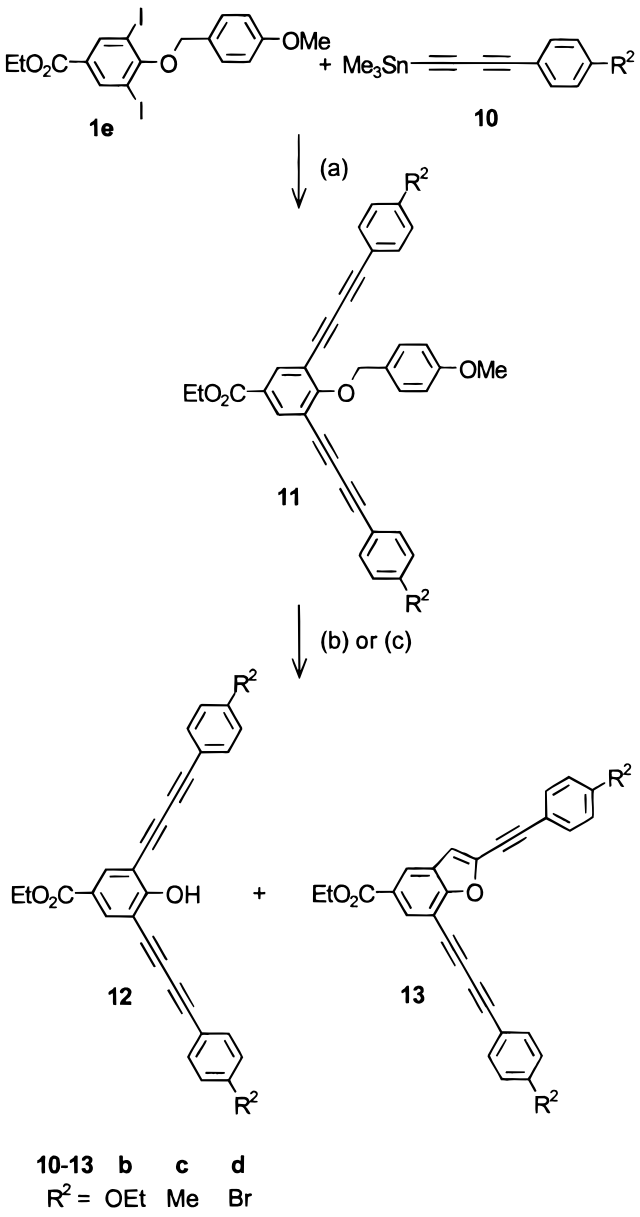
clean reaction of **5c** (one experiment) and **5d** (two experiments) with **1e** resulted. No benzofuran was detected by ^{1}H NMR spectroscopy. The coupling reaction in Et_3N/THF was extremely slow compared to that in piperidine: e.g., the degree of conversion of the coupling of **1e** with **5d** in Et_3N/THF was 23% after 3.5 h and the reaction was still incomplete after 22 h at room temperature, while the reaction in piperidine was quantitative after 2.3 h at room temperature.[20] Nevertheless, the reaction in Et_3N/THF was quantitative after ca. 44 h.

The final step to form the title compounds **8** was the deprotection of the phenolic OH-group. Cleavage of the PMB-ether with ceric ammonium nitrate[21] or with DDQ[22] was very slow and gave side products. A clean and quantitative removal of the PMB-group of **7d** was achieved by heating (60 °C, 5.3 h) **7d** in CH_2Cl_2/EtOH in the presence of concentrated HCl. Applying this procedure (80 °C, 6.5 h) to **7c** gave the hydroxybenzoate **8c** contaminated with ca. 8% of the benzofuran **9c**.[23] Even with the milder procedure described by Akiyama et al.[24] with $SnCl_2$, TMSCl, and anisole as reagents, the formation of the hydroxybenzoate **8c** was accompanied by formation of the benzofuran **9c**. The amount of **9c** depended on the reaction time: After 2, 3.6, and 6 h at room temperature 1%, 3%, and 9% of **9c** were found in the crude products.[19] Chromatography followed by recrystallization gave **8c** with less than 1% of the benzofuran **9c**. Experiments to synthesize the hydroxybenzoate **8b** starting from **7b** proceeded unsatisfactorily by either procedure. Heating **7b** in CH_2Cl_2/EtOH in the presence of concentrated HCl for 2.3 h at 40 °C gave a 4:6 mixture of the hydroxybenzoate **8b** and the benzofuran **9b**. The product obtained from **7b** using $SnCl_2$, TMSCl, and anisole (rt, 45 min) contained, in addition to **8b**, about 15% of **9b** and ca. 8% of an unidentified side product. We did not attempt to isolate the hydroxybenzoate **8b** from these mixtures.

Ethyl 3,5-Di(4-arylbutadiynyl)-4-hydroxybenzoates 12 (Scheme 3). In analogy to the synthesis of the hydroxybenzoates **8** via the PMB-protected hydroxybenzoates **7**, the butadiynylic hydroxybenzoates **12** were synthesized via the PMB-protected hydroxybenzoates **11**. Compounds **11b**−**d** were obtained by coupling the diiodo compound **1e** with 1-aryl-2-(trimethylstannyl)butadiynes **10** in the presence of $Pd_2(dba)_3$ and $AsPh_3$ in refluxing THF.[18] Using the O-unprotected diiodo compound **1a** under the same coupling conditions led to only 30% conversion of **1a**, whereas all the stannylbutadiyne **10b** was used up.

A comparison of the results on PMB-removal from compounds **7b**−**d** shows that compound **7b**, carrying ethoxy substituents, forms benzofuran most easily, while compound **7d**, carrying bromo substituents, resists benzofuran formation under the reaction conditions used for deprotection. Obviously, an increase in electron density in the CC triple bond increases the amount of benzofuran formed. This suggests that the rate-determining step for benzofuran formation is an electrophilic attack at the triple bond. Therefore, because of the lower nucleophilicity of a butadiyne moiety compared to an ethyne moiety, deprotection of the compounds **11b**−**d** was expected to be less troublesome. Indeed, transformation of **11c**,**d** into hydroxybenzoates **12c**,**d** through heating in CH_2Cl_2/EtOH/HCl proceeded cleanly and quantitatively. The same result was obtained using TMSCl/$SnCl_2$/anisole in CH_2Cl_2.[24] However the latter procedure gave considerably lower yields (60−70% compared to 80−90% for the former procedure) due to higher loss of **12c**,**d** upon removing the accompanying product, di(methoxyphenyl)-methane, which formed in the reaction of the PMB-moiety with anisole. Reaction of the donor substituted compound **11b** in refluxing CH_2Cl_2/EtOH/HCl for 18.5 h gave a mixture of the hydroxybenzoate **12b** and the

Scheme 3[a]



[a] Key: (a) $Pd_2(dba)_3$, $AsPh_3$, THF, 60 °C (70−88%); (b) concd HCl, EtOH, CH_2Cl_2, reflux; (**12c**: 81%; **12d**: 90%) (c) TMSCl, $SnCl_2$, anisole, CH_2Cl_2, rt (**12b**: 62%; **12c**: 62%; **12d**: 71%).

(20) Large differences in the reaction rate of alkynyl-aryl-coupling upon varying the amine have been reported: Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

(21) E.g.: (a) Johansson, R.; Samuelsson J., *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371. (b) Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta Chem. Scand.* **1984**, *B38*, 419.

(22) E.g.: Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(23) Formation of benzofuran as a side product upon cleavage of an *o*-alkynylphenyl acetate under acidic conditions was described: Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

(24) Akiyama, T.; Shima, H.; Ozaki, S. *Synlett* **1992**, 415.

benzofuran **13b** (ca. 6%).[13] The formation of **13b** could be avoided by applying the alternative reagents TMSCl/$SnCl_2$/anisole.

Conclusion

We have developed syntheses for 3,5-diaryl-, 3,5-di(arylethynyl)-, and 3,5-di(arylbutadiynyl)-4-hydroxybenzoates **3**, **4**, **8**, and **12**. The *m*-terphenylene compounds **3** were obtained by starting with the diiodo compound **1a** and arylboronic acids. Compound **3c** is of special interest because it allows for an extension of the *m*-terphenylene unit by alkynyl−aryl coupling as shown by the preparation of compounds **4**.

The reaction of **1a** with arylethynes gave primarily benzofuran **9**. The reaction of **1a** with 1-aryl-2-(trimethylstannyl)butadiynes resulted in very low conversion of **1a**. Therefore, to synthesize the acetylenic compounds **8** and **12**, the OH-group of **1a** was protected. PMB was found to be the most suitable protecting group. Removal of the PMB-group from the coupling products **7** and **11** was only achieved under acidic conditions. Depending on the substituents R^2 of the compounds **7** and **11** and on the reaction conditions, this deprotection was accompanied by formation of the benzofurans **9** or **13**.

Experimental Section

General Methods. All reactions were performed under argon. Solutions were degassed, if necessary, through several freeze−pump−thaw cycles. THF was distilled from sodium/benzophenone. Piperidine and triethylamine were dried over CaH_2. $Pd(PPh_3)_2Cl_2$ was synthesized according to the literature,[25] with 2.1 times the amount of methanol, however. Ethyl 3,5-diiodo-4-hydroxybenzoate **1a**,[8] ethyl 3,5-diiodo-4-(4-methoxybenzyloxy)benzoate **1e**,[18] arylethynes **5**,[18] 1-ethoxy-4-iodobenzene,[18] and compounds **11**[18] were synthesized as described. The petroleum ether used had a boiling range of 30−40 °C. For flash chromatography, Merck silica gel (40−63 μm) was used. TLC was carried out on silica gel coated aluminum foils (Merck alumina foils $60F_{254}$). Unless otherwise specified, NMR spectra were recorded in $CDCl_3$ as solvent and internal standard on a 300 MHz spectrometer at room temperature. For signal assignment, the carbon multiplicity was determined by a DEPT experiment. The subscripts α, β, γ, and δ refer to the aromatic rings.The hydroxybenzoate moiety is named with α. The benzene unit of the PMB protecting group is named δ. The benzene unit closest to the hydroxybenzoate moiety is named β and the residual benzene unit is named γ. For the numbering of the positions, the ethyl 4-hydroxybenzoate is considered as the substituted parent compound. The melting points were determined in open capillaries or with a melting table microscope.

1-Bromo-4-(triisopropylsilylethynyl)benzene. To a degassed, cold (ca. 0 °C) solution of 1-bromo-4-iodobenzene (73.84 g, 261 mmol) and triisopropylsilylacetylene (60.9 mL, 272 mmol) in piperidine (300 mL) were added $Pd(PPh_3)_2Cl_2$ (1.83 g, 2.61 mmol) and CuI (994 mg, 5.22 mmol). After the reaction mixture was stirred for 2 h at 0 °C (ice bath) and for a further 15 h at room temperature, diethyl ether and 2 N HCl (exothermic!) were added. The organic phase was washed twice with 2 N HCl, and the combined aqueous phases were extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. Distillation (140−145 °C/0.6 mbar) gave 1-bromo-4-(triisopropylsilylethynyl)benzene (75 g, 85%) as a slightly yellow liquid. The material contained most probably TIPS−C≡C−C≡C-TIPS (3 mol %; ^{1}H NMR: δ = 1.09). Piperidine can be substituted by a 1:1 mixture of THF/piperidine. In several experiments, the addition of further triisopropylsilylacetylene (0.1−0.3 equiv) was necessary to drive the reaction to completion. ^{1}H NMR: δ = 7.42 (half of AA′XX′, 2H, H-2, -6), 7.32 (half of AA′XX′, 2 H, H-3, -5), 1.12 (s, 21 H, C*H*(CH_3)$_2$). ^{13}C NMR: δ = 133.4 (C-3,-5), 131.4 (C-2,-6), 122.5 (C-1,-4), 105.9, 92.0 (*C*≡*C*), 18.6 (CH_3), 11.3 (*C*H). FD-MS: *m*/*z* = 336.5 (100). Anal. Calcd for $C_{17}H_{25}BrSi$ (337.383): C, 60.52, H 7.47, Br 23.68; found C 61.40, H 6.94, Br 23.53;

4-(Triisopropylsilylethynyl)phenylboronic Acid (2c). To a solution of 1-bromo-4-(triisopropylsilylethynyl)benzene (12.5 g, 37.0 mmol) in THF (250 mL) at −78 °C was added 1.6 M *n*-BuLi in hexane (30 mL, 48 mmol). After 30 min at −78 °C, this cold solution was added via a transfer needle to triisopropylborate (25.4 mL, 110 mmol), which was cooled to −45 °C.[12] After complete addition of the aryllithium, the reaction mixture was allowed to reach room temperature and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with 2 N HCl. After the mixture was stirred for 1 h at room temperature, the organic phase was separated and washed with brine. The combined aqueous phases were extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography (petroleum ether/diethyl ether 1:2 v/v → diethyl ether; R_f (Et_2O) = 0.76) gave **2c** (10 g, 90%) as a colorless solid. In most cases, the crude product was used for the reaction with **1a**. ^{1}H NMR (DMSO): δ = 8.16 (s, 2 H,O*H*), 7.77, 7.40 (AA′XX′, 2 H each, Ar*H*), 1.08 (s, 21 H, C*H*(CH_3)$_2$). ^{13}C NMR (DMSO): δ = 134.2, 130.5 (C-2,-6, C-3,-5), 123.7 (C-4), 107.4 and 90.6 (*C*≡*C*), 18.4 (CH_3), 10.7 (*C*H).

Ethyl 3,5-Di[4-(triisopropylsilylethynyl)phenyl]-4-hydroxybenzoate (3c). To the carefully degassed, biphasic mixture of **1a** (2.62 g, 6.28 mmol), 4-(triisopropylsilylethynyl)-phenylboronic acid (**2c**) (5.70 g, 18.9 mmol), and Cs_2CO_3 (8.20 g, 25.2 mmol) in acetone (60 mL) and water (20 mL) was added $Pd_2(dba)_3$ (173 mg, 0.19 mmol). The dark mixture was kept at 65 °C for 18 h. After the mixture was cooled to room temperature, diethyl ether was added. The organic phase was washed with 2 N HCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (petroleum ether/CH_2Cl_2 4:1 v/v; R_f = 0.24) gave **3c** (3.5 g, 81%) as a colorless solid. Mp: 88 °C dec. ^{1}H NMR: δ = 7.95 (s, 2 H, H_α), 7.58, 7.48 (AA′XX′, 4 H each, H_β), 5.68 (s, 1 H, O*H*), 4.35 (q, *J* = 7 Hz, 2 H, CH_2), 1.36 (t, *J* = 7 Hz, 3 H, CH_3), 1.13 (s, 42 H, C*H*(CH_3)$_2$). ^{13}C NMR: δ = 166.1 (CO_2), 153.1 (C_α-4), 136.4 (C_β-1), 132.6 (C_β-3, -5), 131.6 (C_α-2, -6), 129.2 (C_β-2, -6), 128.3 (C_α-3,-5), 123.5, 123.3 (C_α-1, C_β-4), 106.6, 91.9 (*C*≡*C*), 60.9 (CH_2), 18.7 (CH(CH_3)$_2$), 14.4 (CH_2CH_3), 11.3 (Si*C*H). Anal. Calcd for $C_{43}H_{58}O_3Si_2$ (679.106): C, 76.05; H, 8.61. Found: C, 75.95; H, 8.58.

Ethyl 3,5-Di(4-ethynylphenyl)-4-hydroxybenzoate (3d). To a solution of **3c** (3.40 g, 5.00 mmol) in THF (10 mL) was added 1 M *n*-Bu_4NF in THF (10 mL, 10 mmol) at room temperature. A yellow precipitate formed slowly. After 2 h at room temperature, 2 N HCl was added, and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography (petroleum ether/diethyl ether 4:1 v/v; R_f = 0.58) gave **3d** (1.8 g, 99%) as a colorless solid. Mp: 151.4−153.7 °C. ^{1}H NMR: δ = 7.95 (s, 2 H, H_α), 7.60, 7.50 (AA′XX′, 4 H each, H_β), 5.74 (s, 1 H, O*H*), 4.34 (q, *J* = 7 Hz, 2 H, CH_2), 3.13 (s, 2 H, C≡C*H*), 1.36 (t, *J* = 7 Hz, 3 H, CH_3). ^{13}C NMR: δ = 166.0 (CO_2), 153.1 (C_α-4), 136.9 (C_β-1), 132.7 (C_β-3, -5), 131.7 (C_α-2, -6), 129.3 (C_β-2, -6), 128.2 (C_α-3, -5), 123.4 (C_α-1), 122.0 (C_β-4), 83.2, 78.2 (*C*≡*C*H) (both signals appear in the DEPT-135 spectrum with very low intensity), 61.0 (CH_2), 14.4 (CH_3). Anal. Calcd for $C_{25}H_{18}O_3$ (366.416): C, 81.95; H, 4.95. Found: C, 81.92; H, 4.98.

General Comment on the Alkynyl−Aryl Coupling Using $Pd(PPh_3)_2Cl_2$, CuI, and Base. The reaction is slightly exothermic. Therefore, in the case that larger amounts of starting materials and/or smaller amounts of solvent are used, cooling with an ice bath is recommended before the addition of the catalysts.

Ethyl 3,5-Di[4-(4-ethoxyphenylethynyl)phenyl]-4-hydroxybenzoate (4a). To a degassed solution of **3d** (1.50 g, 4.09 mmol) and 1-ethoxy-4-iodobenzene (2.44 g, 9.83 mmol) in piperidine (40 mL) were added $Pd(PPh_3)_2Cl_2$ (69 mg, 0.098 mmol) and CuI (38 mg, 0.199 mmol). A bright yellow precipitate formed. After 16 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, whereupon the precipitate dissolved. The reaction mixture was washed with 2 N HCl (exothermic!), and the combined aqueous phases were extracted with CH_2Cl_2. The

(25) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: 1985; p 18.

combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (petroleum ether/CH_2Cl_2 1:1 v/v; $R_f = 0.35$) gave **4a** (2.0 g, 81%) as a colorless solid. Mp: 200.3−202.2 °C. ^{1}H NMR: $\delta = 7.98$ (s, 2 H, H_α), 7.61, 7.53 (AA′XX′, 4 H each, H_β), 7.46 (half of AA′XX′, 4 H, H_γ-2,-6), 6.86 (half of AA′XX′, 4 H, H_γ-3, -5), 5.77 (br s, 1 H, O*H*), 4.36 (q, $J = 7$ Hz, 2 H, CO_2CH_2), 4.04 (q, $J = 7$ Hz, 4 H, $ArOCH_2$), 1.41 (t, $J = 7$ Hz, 6 H, $ArOCH_2CH_3$), 1.37 (t, $J = 7$ Hz, 3 H, $CO_2CH_2CH_3$). ^{13}C NMR: $\delta = 166.1$ (CO_2), 159.2 (C_γ-4), 153.2 (C_α-4), 135.9 (C_β-1), 133.1 (C_γ-2, -6), 132.0 (C_β-3, -5), 131.6 (C_α-2, -6), 129.3 (C_β-2, -6), 128.3 (C_α-3, -5), 123.6, 123.3 (C_α-1, C_β-4), 115.0 (C_γ-1), 114.6 (C_γ-3, -5), 90.6 (C≡*C*Ar$_\gamma$), 87.6 (*C*≡CAr$_\gamma$), 63.5 ($ArOCH_2$), 60.9 (CO_2CH_2), 14.7 ($ArOCH_2CH_3$), 14.4 ($CO_2CH_2CH_3$). Anal. Calcd for $C_{41}H_{34}O_5$ (606.718): C, 81.17; H, 5.65. Found: C, 81.02; H, 5.71.

Ethyl 3,5-Di[4-(4-nitrophenylethynyl)phenyl]-4-hydroxybenzoate (4b). To a degassed solution of **3d** (600 mg, 1.64 mmol) and 1-iodo-4-nitrobenzene (1.10 g, 4.42 mmol) in THF (15 mL) and triethylamine[26] (20 mL) were added $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol) and CuI (15 mg, 0.08 mmol). After 16 h at room temperature, the reaction was worked up as described for **4a**. Flash chromatography (petroleum ether/CH_2Cl_2 1:3 v/v; $R_f = 0.62$) gave **4b** (880 mg, 80%) as a yellow solid. Mp: 274.6−277.2 °C dec. Anal. Calcd for $C_{37}H_{24}N_2O_7$ (608.606): C, 73.02; H, 3.97; N, 4.60. Found: C, 72.91; H, 4.06; N, 4.45. For NMR data see the Supporting Information.

Ethyl 3,5-Di[2-(4-ethoxyphenyl)ethynyl]-4-(4-methoxybenzyloxy)benzoate (7b). To a degassed solution of **1e** (2.00 g, 3.72 mmol) and (4-ethoxyphenyl)ethyne (**5b**) (1.20 g, 8.21 mmol) in piperidine (20 mL) were added $Pd(PPh_3)_2Cl_2$ (26 mg, 0.037 mmol) and CuI (14 mg, 0.074 mmol). The reaction heat was counterbalanced by cooling with an ice bath for a short time. After 3 h of stirring at room temperature, the reaction mixture was cooled with an ice bath and water was added. The product was extracted into diethyl ether/THF, and the combined organic phases were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated in vacuo. Filtration through silica gel (petroleum ether/diethyl ether 1:1 v/v; $R_f = 0.44$) followed by recrystallization from ethanol gave **7b** (1.2 g, 54%) as an off-white solid, free of benzofuran **9b** (according to ^{1}H NMR spectroscopy). Mp: 144.8−146.4 °C. ^{1}H NMR: $\delta = 8.10$ (s, 2 H, H_α), 7.48, 6.84 (AA′XX′, 2 H each, H_δ), 7.42, 6.87 (AA′XX′, 4 H each, H_β), 5.37 (s, 2 H, OCH_2Ar), 4.37 (q, $J = 7$ Hz, 2 H, CO_2CH_2), 4.06 (q, $J = 7$ Hz, 4 H, $ArOCH_2$), 3.78 (s, 3 H, OCH_3), 1.43 (t, $J = 7$ Hz, 6 H, $ArOCH_2CH_3$), 1.41 (t, $J = 7$ Hz, 3 H, $CO_2CH_2CH_3$). ^{13}C NMR: $\delta = 165.2$ (CO_2Et), 163.3 (C_α-4), 159.6 (C_δ-4), 159.3 (C_β-4), 134.1 (C_α-2, -6), 133.1 (C_β-2, -6), 130.1 (C_δ-2, -6), 129.2 (C_δ-1), 125.9 (C_α-1), 118.4 (C_α-3, -5), 114.9 (C_β-1), 114.6 (C_β-3, -5), 113.7 (C_δ-3, -5), 94.8 and 83.7 (*C*≡*C*), 75.3 (OCH_2Ar), 63.5 ($ArOCH_2CH_3$), 61.2 (CO_2CH_2), 55.2 (OCH_3), 14.7 ($ArOCH_2CH_3$), 14.3 ($CO_2CH_2CH_3$). Anal. Calcd for $C_{37}H_{34}O_6$ (574.673): C, 77.33; H, 5.96. Found: C, 77.30; H, 5.88.

Ethyl 3,5-Di[2-(4-methylphenyl)ethynyl]-4-(4-methoxybenzyloxy)benzoate (7c). To a degassed solution of **1e** (2.00 g, 3.72 mmol) and *p*-tolylethyne (**5c**) (958 mg, 8.25 mmol) in THF (15 mL) and Et_3N (3 mL, 22 mmol) were added $PdCl_2(PPh_3)_2$ (52 mg, 0.074 mmol) and CuI (28 mg, 0.15 mmol), whereupon the reaction mixture turned immediately black. After 44 h of stirring at room temperature, the reaction mixture was cooled with an ice bath, and 2 N HCl was added. The aqueous phase was extracted with diethyl ether. The combined organic phases were washed with 2 N HCl, which was saturated with NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (petroleum ether/diethyl ether 2:1 v/v; $R_f = 0.37$) gave 1.9 g of a light brown solid that was recrystallized from ethanol (100 mL) to yield **7c** (1.53 g, 80%) as a powdery, slightly beige solid. Mp: 126.6−127.2 °C. Anal. Calcd for $C_{35}H_{30}O_4$ (514.621): C, 81.69; H, 5.88. Found: C, 81.77; H, 5.93. For NMR data see the Supporting Information.

Ethyl 3,5-Di[2-(4-methylphenyl)ethynyl]-4-hydroxybenzoate (8c). To a solution of **7c** (1.07 g, 2.08 mmol) in CH_2Cl_2 (23 mL) were added successively anisole (0.7 mL, 6.4 mmol), trimethylsilyl chloride (0.8 mL, 6.3 mmol), and $SnCl_2$ (39 mg, 0.21 mmol) at room temperature. Soon the solution color turned dark-yellow to orange. The reaction mixture was stirred at room temperature for 3.7 h, whereupon water was added. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were washed with water and dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (petroleum ether/CH_2Cl_2 1:1.5 v/v, $R_f = 0.45$) gave **5c** (624 mg) accompanied by reaction products of the protecting group and traces of benzofuran **9c**. Subsequent recrystallization from ethanol (14 mL) gave **8c** (510 mg, 62%), contaminated with less than 1% of benzofuran **9c**, as very fine, colorless needles. Mp: 129.8−130.1 °C. ^{1}H NMR: $\delta = 8.10$ (s, 2 H, H_α), 7.45, 7.17 (AA′XX′, 4 H each, H_β), 6.61 (s, 1 H, O*H*), 4.36 (q, $J = 7$ Hz, 2 H, CH_2), 2.37 (s, 6 H, $ArCH_3$), 1.39 (t, $J = 7$ Hz, 3 H, CH_2CH_3). ^{13}C NMR: $\delta = 165.1$ (CO_2Et), 160.0 (C_α-4), 139.2 (C_β-4), 133.9 (C_α-2,-6), 131.6 (C_β-2, -6), 129.2 (C_β-3, -5), 123.1 (C_α-1), 119.2 (C_β-1), 110.6 (C_α-3, -5), 96.3, 81.9 (*C*≡*C*), 61.1 (CH_2), 21.5 ($ArCH_3$), 14.3 (CH_2CH_3). Anal. Calcd for $C_{27}H_{22}O_3$ (394.470): C, 82.21; H, 5.62. Found: C, 82.22; H, 5.73.

Ethyl 3,5-Di[2-(4-bromophenyl)ethynyl]-4-hydroxybenzoate (8d). A solution of **7d** (1.00 g, 1.55 mmol) in CH_2Cl_2 (20 mL), ethanol (5 mL), and concentrated HCl (0.9 mL) was stirred at 60 °C for 5.7 h. After the solution was cooled to room temperature, water was added, and the organic phase was washed with water, dried ($MgSO_4$), and concentrated in vacuo. From the thus-obtained solid, 4-methoxybenzyl alcohol and 4-methoxybenzylethyl ether were distilled off (40−45 °C bath temperature/0.001 mbar) to give **8d** (752 mg, 92%) as an off-white residue. Mp: 167−168 °C. Anal. Calcd for $C_{25}H_{16}Br_2O_3$ (524.220): C, 57.28; H, 3.08. Found: C, 57.27; H, 3.00. For NMR data see the Supporting Information.

Alternatively, the deprotection of **8d** (1.10 g, 1.71 mmol) was achieved as described for **8c** with TMSCl, $SnCl_2$, and anisole. The crude product was suspended in diethyl ether to give **8d** (563 mg, 63%) as a colorless solid.

Ethyl 3,5-Di[4-(4-ethoxyphenyl)butadiynyl]-4-hydroxybenzoate (12b). To a solution of **11b** (620 mg, 1.00 mmol) in CH_2Cl_2 (12 mL) were added successively anisole (0.4 mL, 3.7 mmol), trimethylsilyl chloride (0.4 mL, 3.5 mmol), and $SnCl_2$ (19 mg, 0.1 mmol) at room temperature. Soon the solution turned dark-yellow to orange colored. The reaction mixture was stirred at room temperature for 2 h, whereupon water was added. The aqueous phase was saturated with NaCl and then extracted with THF. The combined organic phases were washed with brine and dried (Na_2SO_4), and the solvent was removed in vacuo. The solid residue was suspended in diethyl ether (7 mL) to give **12b** (442 mg) accompanied by traces of products resulting from the protecting group. Subsequent recrystallization from ethanol containing some acetone gave **12b** (326 mg, 62%; the yield was calculated by taking into account the amount of residual solvent determined by ^{1}H NMR spectroscopy) as a yellow powder containing ethanol (ca. 4%). Ethanol could be exchanged against THF by dissolving the product in THF and removing the solvent in vacuo. Attempts to remove residual THF at room temperature failed. In one experiment, THF was removed by keeping the compound at 70 °C/10^{-2} mbar for several hours. However, because **12b** occasionally isomerized on heating, it is advisable, if possible, to use the compound containing residual solvent. ^{1}H NMR: $\delta = 8.10$ (s, 2 H, H_α), 7.46, 6.85 (AA′XX′, 4 H each, H_β), 6.52 (s, 1 H, O*H*), 4.34 (q, $J = 7$ Hz, 2 H, CO_2CH_2), 4.04 (q, $J = 7$ Hz, 4 H, $ArOCH_2$), 1.42 (t, $J = 7$ Hz, 6 H, $ArOCH_2CH_3$), 1.37 (t, $J = 7$ Hz, 3H, $CO_2CH_2CH_3$). ^{13}C NMR: $\delta = 164.6$ (CO_2Et), 162.6 (C_α-4), 160.2 (C_β-4), 135.5 (C_α-2, -6), 134.3 (C_β-2, -6), 123.5 (C_α-1), 114.8 (C_β-3, -5), 112.9 (C_β-1), 109.7 (C_α-3, -5), 84.2, 81.0 (C≡C−C≡*C*), 73.9, 72.1 (C≡*C*−*C*≡C), 63.7 ($ArOCH_2$), 61.3 (CO_2CH_2), 14.7 ($ArOCH_2CH_3$), 14.3 ($CO_2CH_2CH_3$). FD-MS: $C_{33}H_{26}O_5$ (502.566) $m/z = 502.7$ (100).

Ethyl 3,5-Di[4-(4-methylphenyl)butadiynyl]-4-hydroxybenzoate (12c). A solution of **11c** (347 mg, 0.62 mmol) in CH_2Cl_2 (20 mL), ethanol (5 mL), and concentrated HCl (0.9 mL) was refluxed for 17 h. After the solution was cooled to room temperature, water was added, the aqueous phase was extracted with THF, and the combined organic phases were washed with brine and finally dried (Na_2SO_4). Removal of solvent in vacuo was followed by recrystallization in ethanol (ca. 70 mL) to give **12c** (220 mg, 81%) containing ethanol. Ethanol could be exchanged against THF by dissolving the product in THF and

(26) Use of piperidine instead of triethylamine resulted in addition of piperidine onto the triple bond of the coupling product **4b**.

removing the solvent in vacuo. However, then THF (13%) was tightly included: Even after heating the product to 60 °C/0.01 mbar for 7h, the powder contained THF. FD-MS: $C_{31}H_{22}O_3$ (442.514) m/z = 221.2 (3), 442.5 (100), 885.8 (5). For NMR data see the Supporting Information.

Alternatively, the deprotection of **11c** (1.95 g, 3.46 mmol) was achieved as described for **12b** with TMSCl, $SnCl_2$, and anisole. The crude product was suspended in diethyl ether. The precipitate was isolated from the cold (−78 °C) suspension and recrystallized from ethanol (150 mL)/acetone (50 mL) to give **12c** (1.1 g, 62%) as a pale yellow powder.

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Supporting Information Available: Detailed experimental procedures and full characterization of the compounds **1d**, **3a**,**b**, **7d**, and **12d**, NMR data of **4b**, **7c**, **8d**, and **12c**, as well as analytical data of the benzofurans **9c** and **13c** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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