Arylation of Phenols. Convenient, Regiospecific Methods for Mono- or Bis-*p*-fluorophenylations, Suitable for Large Scale Syntheses

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Phenols have been arylated by a palladium(0)-catalyzed coupling reaction. Two methods were used: a Grignard reagent of a protected phenol component **2** was coupled with a haloarene, or an umpolung (reversed reactivity) where unprotected phenolic halides **6** were coupled with aryl Grignard reagents. Bis-arylation and regiospecific *ortho*-, *meta*- and *para*-arylations were achieved. Aryl–aryl couplings were insensitive to steric hindrance in the Grignard component, but were inhibited by sulfur-containing substituents in the phenolic component. A thiocyanate substituted biaryl was used to synthesize arylated phenols with various sulfur functionalities.

Until recently there was no general method for the direct arylation of phenols.[2] In 1985, Barton and co-workers published on the regiospecific *ortho*-phenylation of phenols with triphenylbismuth(V) dichloride or pentaphenylbismuth in the presence of a base.[3]

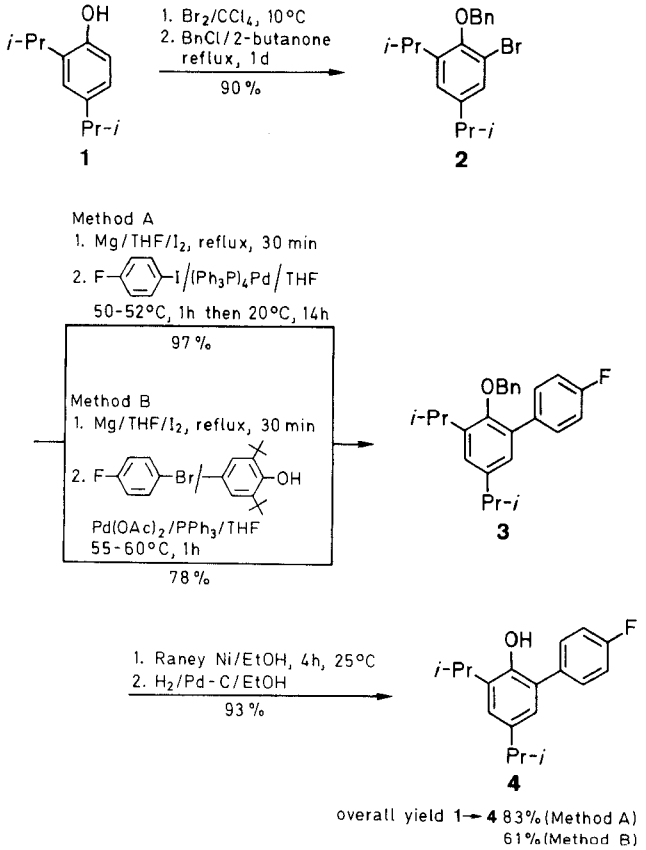
Although this elegant reaction proceeds under very mild conditions, it has disadvantages:

1. Yields are excellent for the activated β-naphthol, but unsatisfactory (20–50%) for other phenols.[3]
2. Bismuth(V) reagents and the preferred base *N-tert*-butyl-*N'*,*N''*-tetramethylguanidine (BTMG) are not commercially available. The bismuth(V) reagents are prepared from commercially inaccessible triphenylbismuth.[3,4]
3. No data is available on the compatibility of phenyl substituents with the bismuthation reaction.

In the last decade, the methodology of palladium(0)-catalyzed couplings has developed to one of the most powerful tools in organic synthesis.[5,6] Despite the high tolerance of oxygen functionalities in palladium-catalyzed bond formation,[7] known aryl–aryl couplings[5,6,8,9] were never extended to the arylation of phenols.

In this paper we describe two procedures for fluorophenylation of substituted phenols. The methods (Schemes **A** and **B**) are complementary to each other.

1. The method, depicted in Scheme **A** uses a protected phenol **2**, while in Scheme **B** the palladium-catalyzed arylations are performed with the free phenol **6**.
2. In Scheme **A** the Grignard reagent of the protected phenol is coupled with a haloarene, whereas in Scheme **B** the coupling is reversed: halogenated phenols are coupled with arylmagnesium halides.



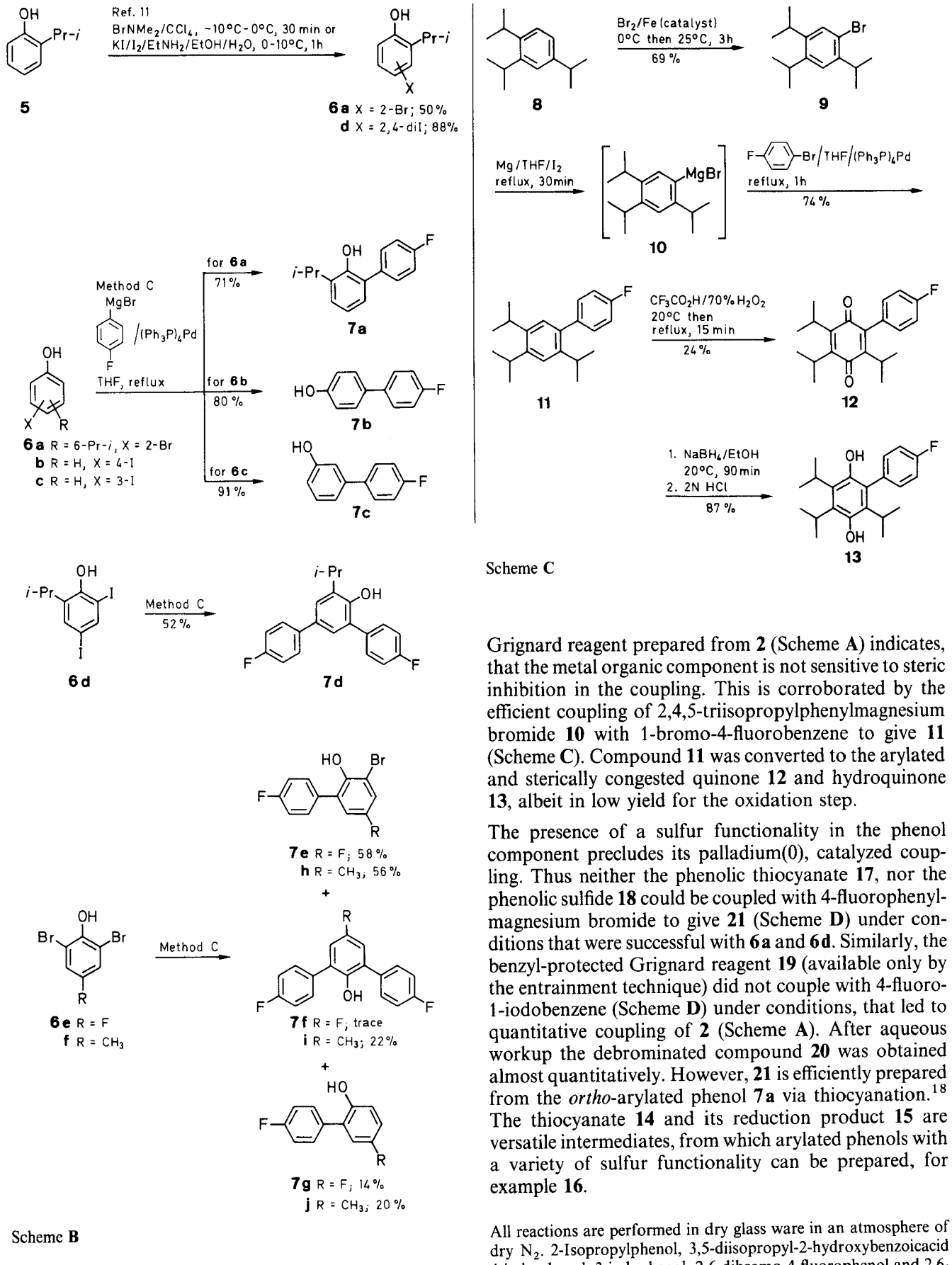
Scheme A

The reversal allows double-arylations,[10] for example **7d** as well as regiospecific *ortho*-arylations,[11,12] for example **7a**, of phenols with unsubstituted *meta*- and/or *para*-positions (e.g. **5**) to be conducted (Table 1). Capillary-GC of the *ortho*-arylated phenol **7a** indicates a purity of > 99.9%. This demonstrates the high regioselectivity of the bromination[11] as well as the subsequent arylation. *para*-Arylation **7b** or *meta*-arylation **7c** is also achieved in excellent yield. The diiodophenol **6d** exhibits a double-coupling to give **7d** as the major product. However, the dibromophenols **6e** and **6f** gave the products of monocoupling **7e,h** as the major product with either traces **7f** or small amounts **7i** of double-coupling products.

Products from the exchange of the second bromo atom for hydrogen were observed under forcing conditions, although to a limited extend (**7g**, 14%; **7i**, 20%).

The methods exemplified in Schemes **A** and **B** share some properties, that render them synthetically attractive:

1. All reagents are commercially available.
2. The arylation reactions are highly catalytic in the palladium(0) complex.[15] The palladium(0)-catalyst can be substituted (with only a slight yield decrease) by a cheaper palladium diacetate/triphenylphosphine mixture[16], that forms a catalytically active species *in situ* (Scheme **A**, Method B).
3. The more reactive iodoarenes[17] can be replaced by cheaper bromoarenes[16] (Scheme A, Method B, and Scheme **B**, Method C).
4. The reactions have been conveniently conducted on large scale under laboratory conditions to give the arylated phenols **4**, **7a**, **7d**, and **14** in 100 g to 1 kg quantities (see experimental).



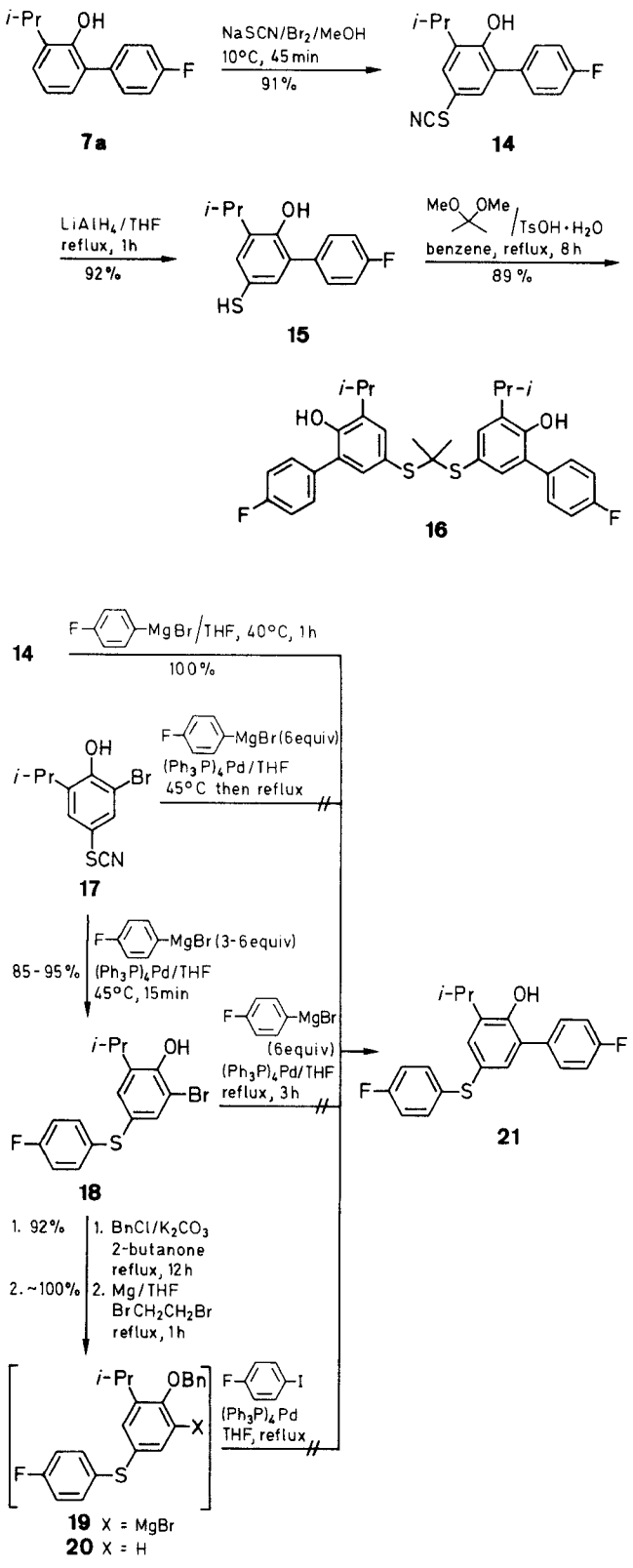
Scheme B

Scheme C

The yields of known palladium(0)-catalyzed aryl–aryl couplings fall severely when bulky substituents are present close to the halogen atom in the haloarene.[5,9] Contrary, the nearly quantitative yield in the reaction of the Grignard reagent prepared from **2** (Scheme **A**) indicates, that the metal organic component is not sensitive to steric inhibition in the coupling. This is corroborated by the efficient coupling of 2,4,5-triisopropylphenylmagnesium bromide **10** with 1-bromo-4-fluorobenzene to give **11** (Scheme **C**). Compound **11** was converted to the arylated and sterically congested quinone **12** and hydroquinone **13**, albeit in low yield for the oxidation step.

The presence of a sulfur functionality in the phenol component precludes its palladium(0), catalyzed coupling. Thus neither the phenolic thiocyanate **17**, nor the phenolic sulfide **18** could be coupled with 4-fluorophenylmagnesium bromide to give **21** (Scheme **D**) under conditions that were successful with **6a** and **6d**. Similarly, the benzyl-protected Grignard reagent **19** (available only by the entrainment technique) did not couple with 4-fluoro-1-iodobenzene (Scheme **D**) under conditions, that led to quantitative coupling of **2** (Scheme **A**). After aqueous workup the debrominated compound **20** was obtained almost quantitatively. However, **21** is efficiently prepared from the *ortho*-arylated phenol **7a** via thiocyanation.[18] The thiocyanate **14** and its reduction product **15** are versatile intermediates, from which arylated phenols with a variety of sulfur functionality can be prepared, for example **16**.

All reactions are performed in dry glass ware in an atmosphere of dry N_2. 2-Isopropylphenol, 3,5-diisopropyl-2-hydroxybenzoicacid 4-iodo phenol, 3-iodophenol, 2,6-dibromo-4-fluorophenol and 2,6-dibromo-4-methylphenol were purchased from Aldrich. 2-Bromo-6-isopropylphenol was obtained by literature methods;[11] bp 120–122°C/28 mbar. GC used a 30 m fused silica column DB-5 polydiphenyldimethylsiloxane, stationary phase 25 µm, column i.d. 0.32 nm.



Scheme D

2,4-Diiodo-6-isopropylphenol (6d):
70% aq $EtNH_2$ (2.05 L) is added to the solution of 2-isopropylphenol **5** (244 g, 1.79 mol) in EtOH (2.15 L), and the mixture is cooled to −10 °C. The solution of I_2 (957 g, 3.77 mol) and of KI (1000 g, 6.02 mol) in H_2O (1.43 L) is added dropwise within 30 min, keeping the reaction temperature below +10 °C. The mixture is stirred 30 min at 0 °C. Sat. aq $Na_2S_2O_3$ (1.15 L) and H_2O (3 L) is added, and the mixture is extracted with Et_2O (3 × 2 L). The combined extracts are washed with 2 N HCl (6 L) and with H_2O (7 L), dried ($MgSO_4$), and the solvent is evaporated *in vacuo* (bath < 20 °C). Solvent traces are removed under high vacuum to give a red oil; yield: 654 g (94%). This oil is pure according to TLC (100% toluene) and ^{1}H-NMR. It can be distilled through a 15 cm Vigreux column (bp 138 °C/0.53 mbar, recovery 88%), but the yield of Pd (0) cat coupling reactions is virtually identical for distilled and crude **6d**.

2,4-Diisopropylphenol (1):
A suspension of 2-hydroxy-3,5-diisopropylbenzoic acid (500 g, 2.24 mol) and cupric chromite (2 $CuO \cdot Cr_2O_3$, 15.0 g, 0.045 mol) in quinoline (1.08 L, 9.1 mol) is heated with stirring to 195 °C (210 °C bath) for 2 h. At 15–23 °C the mixture is acidified with 6 M HCl (~1.6 L) to pH 1–2. It is extracted twice with toluene (500 mL). The combined extracts are washed with 5N HCl (200 mL), 2N HCl (200 mL), sat. $NaHCO_3$ (200 mL), and dried ($MgSO_4$). The solvent is evaporated and the residue is distilled through a 15 cm Vigreux column to give a colorless oil; yield: 395.5 g (99%); bp 88–92 °C/0.3 mbar.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (d, 6H, J = 7.0 Hz, CH_3), 1.25 (d, 6H, J = 7.0 Hz, CH_3), 3.00 (2 × sept, 2H, CH), 4.10 (br s, 1H, OH), 6.5–7.0 (m, 3 H_{arom}).

MS (70 eV): m/z (%) = 178 (M^+, 100), 163 ($M^+ - CH_3$, 31).

1-Benzyloxy-2-bromo-4,6-diisopropylbenzene (2):
2-Bromo-4,6-diisopropylphenol:
Br_2 (118.6 mL, 367.7 g, 2.3 mol) is added dropwise at 10 °C to the solution of **1** (390 g, 2.18 mol) in CCl_4 (2 L). The solution is washed twice with aq $NaHSO_3$ (500 mL), with H_2O (200 mL), then with brine (200 mL) and dried ($MgSO_4$). The solvent is evaporated and the residue is filtered with cyclohexane/toluene (4:1) through silica gel (1.8 kg) to give 2-bromo-4,6-diisopropylphenol; yield: 556.7 g (99%).

1-Benzyloxy-2-bromo-4,6-diisopropylbenzene (**2**):
Pulverized K_2CO_3 (738 g, 5.35 mol) is added to the solution of this oil (550 g, 2.14 mol) in 2-butanone (2.5 L). Benzyl chloride (406 g, 3.21 mol) is added and the mixture is refluxed for 1 d. Inorganic salts are removed by filtration and washed with acetone (200 mL). The combined filtrates are evaporated. The residue is dissolved in toluene (2 L), washed with H_2O (2 × 500 mL), with brine (200 mL), and dried ($MgSO_4$). The solvent is evaporated and the residue is distilled through a 15 cm Vigreux column to give a colorless oil; yield: 666.0 g (90%); bp 159–162 °C/0.5 mbar.

$C_{19}H_{23}BrO$	calc.	C 65.71	H 6.67	Br 23.01
(347.3)	found	65.59	6.82	22.85

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.18 (d, 6H, J = 7.0 Hz, CH_3), 1.22 (d, 6H, J = 7.0 Hz, CH_3), 2.80 (sept, 1H, CH), 3.32 (sept, 1H, CH), 4.90 (s, 2H, CH_2), 6.93–7.60 (m, 7 H_{arom}).

MS (70 eV): m/z (%) = 346/348 (M^+, 1), 267 (5), 254/256 (2), 91 (100).

1-Benzyloxy-6-(*p*-fluorophenyl)-2,4-diisopropylbenzene (3):
Method A: *2-Benzyloxy-3,5-diisopropylphenylmagnesium Bromide:* A suspension of magnesium turnings (3.53 g, 147 mmol) in dry THF (20 mL) is activated with I_2 crystals. A few drops of **2** are added, possibly with warming, until the exothermic Grignard reaction starts. The solution of **2** (48.62 g, 140 mmol) in dry THF (100 mL) is added dropwise at a rate that maintains a gentle reflux. Subsequently the mixture is refluxed for 30 min.

Reaction of Grignard with 4-fluoro-1-iodobenzene:
In a second flask, a solution of 4-fluoro-1-iodobenzene (31.08 g, 140 mmol) in THF (140 mL) is purged with N_2 for 15 min. $(PPh_3)_4Pd$ (3.23 g, 2.8 mmol) is added, minimizing air-contact.[15] The solution is stirred for 15 min. The above prepared Grignard solution (20 °C) is added at once. The temperature of the reaction mixture rises from 20 °C to 55–60 °C within 15 min; a precipitate is formed after ~7 min. The mixture is stirred at 50–52 °C for 1 h, then allowed to stand overnight at ~20 °C under N_2. The reaction

mixture is divided between Et_2O (500 mL) and 1 N HCl (500 mL). The organic phase is washed with 1 N HCl (250 mL), with H_2O (250 mL), then with sat. $NaHCO_3$ (250 mL), and dried ($MgSO_4$). The solvent is evaporated and the residue is chromatographed on silica gel (500 g) with cyclohexane/toluene (4:1) as eluent (R_f = 0.47). Colorless crystals are obtained; yield: 49.3 g (97%); mp 66–67 °C.

$C_{25}H_{27}FO$	calc.	C 82.84	H 7.51	F 5.24
(362.5)	found	82.82	7.59	5.13

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.30 (2 × d, 12 H, CH_3), 2.95 (sept, 1 H, CH), 3.45 (sept, 1 H, CH), 4.40 (s, 2 H, CH_2), 6.90–7.80 (m, 11 H_{arom}).

MS (DCI, isobutane): m/z (%) = 363 ($M + H^+$, 67), 362 (M^+, 100), 285 (20), 263 (45).

Method B: The Grignard reagent is prepared as described in method A from Mg (46.6 g, 1.94 mol) and **2** (662 g, 1.91 mol) in THF (2 L).

In a second flask a mixture of 1-bromo-4-fluorobenzene (350 g, 2.0 mol), 2,6-di-*tert*-butyl-4-methylphenol (20 mg), $Pd(OAc)_2$ (12.2 g, 40 mmol) and PPh_3 (21.0 g, 80 mmol) in dry THF (1.2 L) is purged with N_2 and stirred at 25 °C for 1 h.

The Grignard solution is cooled to 35 °C and then added at once to this mixture. Within 15 min the temperature rises from 40 °C to 65 °C. Intensive cooling is necessary beginning at 55 °C to maintain a controlled reflux. The mixture is held 1 h at 55–60 °C, then cooled. It is poured into 2 N HCl (3 L)/ice (3 kg) and extracted with toluene (2 × 2 L). The extract is washed with 1 N HCl (1 L), brine (1 L) and sat. $NaHCO_3$ (500 mL), dried ($MgSO_4$) and evaporated. To the residue is added K_2CO_3 (6 g) and it is distilled through a 15 cm Vigreux column, using a Wood's metal bath.

The product is obtained as a colorless oil that crystallizes slowly at 25 °C; yield: 535.4 g (78%); bp 194–198 °C/1.6 mbar. The physical data are identical with those of material prepared according to method A.

6-*p*-Fluorophenyl-2,4-diisopropylphenol (4):

Raney nickel (200 g wet) is washed with EtOH (3 × 1 L) and decanted. The solution of **3** (535 g, 1.48 mol) in abs. EtOH (5 L) is added and the mixture is stirred for 4 h at 25 °C. The metal is removed with suction-filtration and washed with EtOH (2 L). To the combined filtrates is added 10% Pd–C (20 g). The suspension is degassed by applying vacuo and releasing it with N_2 (3 cycles). Then the suspension is shaken under 1 atm of H_2 until the theoretical amount (33.2 L) of H_2 has been taken up. The catalyst

Table. Mono- or Bis(4-fluorophenyl)phenols **7** Prepared

Product	Yield[a] (%)	mp (°C)[b] bp (°C)/mbar	Molecular Formula[c] or Lit. mp (°C)	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS (DCI)[e] m/z (%)
7a	71	45–46 108/0.7	$C_{15}H_{15}FO$ (230.3)	1.28 (d, 6 H, J = 7.0, CH_3), 3.32 (sept, 1 H, CH), 5.08 (s, 1 H, OH), 6.9–7.5 (m, 7 H_{arom})	231 ($M + H^+$, 75), 230 (M^+, 100), 215 ($M^+ - CH_3$, 98)
7b	80	168–169	167–168[13]	4.80 (s, 1 H, OH), 6.73–7.70 (m, 8 H_{arom})	189 ($M + H^+$, 67), 188 (M^+, 100)
7c	91	78–79	77–79[14]	4.86 (s, 1 H, OH), 6.70–7.80 (m, 8 H_{arom})	189 ($M + H^+$, 100), 188 (M^+, 81)
7d	52	76–77	$C_{21}H_{18}F_2O$ (324.4)	1.35 (d, 6 H, J = 7.0, CH_3), 3.40 (sept, 1 H, CH), 5.10 (s, 1 H, OH), 6.8–7.6 (m, 10 H_{arom})	324 (M^+, 100), 309 ($M^+ - CH_3$, 45), 230 ($M^+ - C_6H_3F$, 17), 215 ("230"-CH_3, 36)
7e	58	85–86	$C_{12}H_7BrF_2O$ (285.2)	5.47 (s, 1 H, OH), 6.99 (dd, 1 H_{arom}, J = 8.8, 3.2), 7.13 (AA'BB', 2 H_{arom}), 7.22 (dd, 1 H_{arom}, J = 7.2, 3.2), 7.49 (AA'BB', 2 H_{arom})	287/285 ($M + H^+$, 100), 286/284 (M^+, 93)
7f	trace[f]	–	$C_{18}H_{11}F_3O$ (300.3)	–	300 (M^+, 91), 280 ($M^+ - HF$, 26), 262 (46), 261 (100), 251 (68)
7g	14	69–70	$C_{12}H_8F_2O$ (206.2)	4.87 (s, 1 H, OH), 6.86–7.00 (m, 3 H_{arom}), 7.12–7.22 (AA'BB', 2 H_{arom}), 7.39–7.48 (AA'BB', 2 H_{arom})	207 ($M + H^+$, 100), 206 (M^+, 79), 177 (14)
7h	56	oil	$C_{13}H_{10}BrFO$ (281.1)	2.32 (s, 3 H, CH_3), 5.50 (s, 1 H, OH), 7.03 (d, 1 H_{arom}, J = 2.0), 7.12 (AA'BB', 2 H_{arom}), 7.29 (d, 1 H_{arom}, J = 2.0), 7.50 (AA'BB', 2 H_{arom})	281/283 ($M + H^+$, 62), 280/282 (M^+, 100)
7i	22	111–112	$C_{19}H_{14}F_2O$ (296.3)	2.34 (s, 3 H, CH_3), 5.05 (s, 1 H, OH), 7.05 (s, 2 H_{arom}), 7.14 (AA'BB', 4 H_{arom}), 7.50 (AA'BB', 4 H_{arom})	297 ($M + H^+$, 100), 296 (M^+, 85)
7j	20	oil	$C_{13}H_{11}FO$ (202.2)	2.32 (s, 3 H, CH_3), 4.88 (s, 1 H, OH), 6.87 (d, 1 H_{arom}, J = 8.0), 7.01–7.09 (m, 2 H_{arom}), 7.17 (AA'BB', 2 H_{arom}), 7.45 (AA'BB', 2 H_{arom})	203 ($M + H^+$, 81), 202 (M^+, 100)

[a] Yield of isolated product **7** based on **6**.
[b] Recrystalized from cyclohexane; uncorrected. Measured with a Büchi capillary melting point apparatus (according to Dr. Tottoli).
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, Br ±0.25, F ±0.20.
[d] Obtained on a Bruker WP 60 or WM 270 spectrometer.
[e] Recorded on a MS 80 mass spectrometer using positive, desorptive chemical ionization (isobutane).

is filtered off and washed with EtOH. The filtrates are evaporated and the residue is distilled through a 15 cm Vigreux column to give a colorless oil, that crystallizes slowly at 0 °C, yield: 374.9 g (93%); bp 120–122 °C/0.2 mbar; mp ~ 20 °C. TLC (silica, cyclohexane/toluene 10:1): R_f = 0.27

$C_{18}H_{21}FO$	calc.	C 79.38	H 7.77	F 6.98
(272.4)	found	79.21	7.89	6.85

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.25 (d, 6 H, J = 7.0 Hz, CH_3), 1.29 (d, 6 H, J = 7.0 Hz, CH_3), 2.87 (sept, 1 H, CH), 3.31 (sept, 1 H, CH), 4.95 (br s, 1 H, OH), 6.88 (d, 1 H_{arom}, J = 2.0 Hz), 7.08 (d, 1 H_{arom}, J = 2.0 Hz, 7.18 (m, 2 H_{arom}), 7.45 (m, 2 H_{arom}).

MS (70 eV): m/z (%) = 272 (M^+, 41), 257 ($M^+ - CH_3$, 100).

2-(*p*-Fluorophenyl)-6-isopropylphenol (7a); Typical Procedure:
Method C: A THF solution of 4-fluorophenylmagnesium bromide is prepared as described above (Method A) from 1-bromo-4-fluorobenzene (2.446 kg, 13.98 mol, 3.00 equiv.) and magnesium turnings (343.2 g, 14.12 mol, 3.03 equiv.) in dry THF (5 L) in a flask containing a septum.

In a 10 L-flask with mechanical stirrer, reflux condenser with N_2-inlet and bubbler, and septum, a solution of 2-bromo-6-isopropylphenol **6a** (1.002 kg, 4.66 mol, 1.00 equiv.) in THF (1 L) is purged with N_2 for 15 min. $(PPh_3)_4Pd$ (50.0 g, 43.3 mmol, 9×10^{-3} equiv.) is added, minimizing air-contact[15], and the resulting solution is stirred for 15 min. The Grignard solution (30 °C) is transferred with a slight N_2-pressure via cannular ("flex-needle")[19] into this solution. Initially the strongly exothermic reaction raises the temperature to reflux. The rate of transfer is controlled to maintain a gentle reflux. After transfer of one third of the Grignard solution the reaction is only slightly exothermic. Reflux is maintained with an external heating bath and the transfer rate is increased (total transfer time: 1 h). The mixture is refluxed for 4 h, then poured into conc. HCl (1 L)/ice (6 kg) and stirred for 20 min. The organic phase is washed with conc. HCl (500 mL), with brine (500 mL), dried ($MgSO_4$), filtered. The solvent of the filtrate is evaporated and the residue is distilled *in vacuo* through a 30 cm Vigreux column and a Claisen condenser that is cooled initially, and is heated to 50 °C when the distillate starts to crystallize. After a prerun (bp. 115–145 °C/37 mbar and 76–100 °C/1.0 mbar, together 388 g, mainly 4,4'-difluorobiphenyl) is obtained a colorless solid; yield: 761.9 g (71%); bp 116–117 °C/1.0 mbar, mp 45–46 °C (Table). Purity according to GC (180 °C injector 240 °C, 1 bar H_2, t_{ret} 4.46 min): > 99.0%.

For the coupling reactions of phenols **6b–6f** the following equivalents of 4-fluorophenylmagnesium bromide and reflux times were applied:
6b: 2.5 equiv Grignard reagent, 5 min reflux; **6c**: 2.25 equiv, 5 min; **6d**: 4.0 equiv, 1 h; **6e**: 4.5 equiv, 5 h; **6f**: 4.5 equiv, 5 h.

Compounds **7b–j** were purified by chromatography on silica gel. The purity of **7e** was 98.4% by GC (150 °C/5 min, 10 °C/min to 250 °C, injector 240 °C, 1 bar H_2, t_{ret} 8.91 min). The purity of **7g** was 99.6% by GC (conditions as for **7e**, t_{ret} 5.36 min). Compound **7f** was observed by GC/MS (120 °C/2 min with 10 °C/min to 280 °C, 1 bar He, t_{ret} **7e**: 11.15 min, t_{ret} **7f**: 15.75 min) with 15% unreacted dibromophenol **(6e)** (t_{ret} 6.57 min).

1-Bromo-2,4,5-triisopropylbenzene (9):
Iron powder (10 mg) is added to the solution of 1,2,4-triisopropylbenzene[20] (301.3 g, 1.47 mol) in CCl_4 (600 mL). The solution of Br_2 (76 mL, 236.3 g, 1.48 mmol) in CCl_4 (600 mL) is added dropwise at − 10 °C with exclusion of light. Initially there is no significant HBr evolution and the reaction mixture retains its Br_2 color. After complete addition the temperature is raised to 0 °C and a vigorous HBr evolution starts. The mixture is stirred at ambient temperature for 90 min. TlC (cyclohexane) indicates nearly complete conversion of the starting material (R_f = 0.51) to the product (R_f = 0.57) and a byproduct (R_f = 0.64). The reaction mixture is divided between CH_2Cl_2 (2 L) and 10% aq $Na_2S_2O_3$ (500 mL). The organic phase is washed with brine, dried ($MgSO_4$), and the solvent is evaporated.

The residue is distilled in vacuo through a 20 cm Vigreux column to give after a prerun (5.3 g colorless oil, bp 71–103 °C/1.3 mbar) the title compound **9** as a colorless oil (288.9 g, 69%, bp 89–92 °C/0.3 mbar), followed by a yellow oil (25.8 g, bp 98–110 °C/0.3 mbar) consisting of the byproduct and some **9**.

The purity of **9** in the main fraction is 98.4% (GC, 160 °C, 1 bar He, t_{ret} 8.81 min).

$C_{15}H_{23}Br$	calc.	C 63.61	H 8.18	Br 28.21
(283.3)	found	63.49	8.19	28.32

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.24 (d, 18 H, CH_3), 3.19 (sept, 1 H, CH), 7.12 (s, 1 H_{arom}), 7.33 (s, 1 H_{arom}).

MS (DCI, isobutane): m/z (%) = 283/285 ($M + H^+$, 67/50), 282/284 (M^+, 89/100), 267/269 ($M^+ - CH_3$, 48), 241/243 (100/92).

1-(*p*-Fluorophenyl)-2,4,5-triisopropylbenzene (11):
The Grignard reagent **10** is prepared from **9** (251 g, 0.89 mol), Mg turnings (22.3 g, 0.92 mol) in THF (500 mL) according to the method described for **3**, Method A (vide supra). In a second flask the solution of 1-bromo-4-fluorobenzene (162.6 g, 0.93 mol) in THF (800 mL) is purged with N_2. $(PPh_3)_4Pd$ (10.0 g, 8.6 mmol) is added and the solution is stirred for 10 min. The solution of **10** (40 °C) is transferred into this solution via flex-needle.[19]

The mixture is refluxed for 2 h, a colorless precipitate being formed. The cold mixture is divided between Et_2O (1 L) and 2 N HCl (500 mL), the precipitate being removed by decantation. The organic phase is washed with 2 N HCl (500 mL), H_2O (250 mL), sat. $NaHCO_3$ (250 mL), and brine (250 mL), dried ($MgSO_4$), and the solvent is evaporated.

The residue is distilled without column, using a short, air-cooled condenser to give a colorless solid; yield: 196.6 g (74%); bp 114 °C/0.07 mbar, mp 82–83 °C from MeOH).

$C_{21}H_{27}F$	calc.	C 84.52	H 9.12	F 6.37
(298.4)	found	84.49	9.19	6.25

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.10–1.36 (3 × d, 18 H, CH_3), 2.80–3.56 (m, 3 H, CH), 6.86–7.40 (m, 6 H_{arom}).

MS (DCI, isobutane): m/z (%) = 299 ($M + H^+$, 62), 298 (M^+, 100), 257 ($M^+ - C_3H_5\cdot$, 46).

2-(*p*-Fluorophenyl)-3,5,6-triisopropyl-1,4-benzoquinone (12):
In a flask with mechanical stirrer, highly efficient reflux condenser, dropping funnel and inner thermometer, the solution of 70% aq H_2O_2 (68 mL) in trifluoroacetic acid (333 mL) is added dropwise at − 20 °C with stirring to **11** (60.0 g, 201 mmol). The cooling-bath is removed, but kept ready for immediate use. Within 30 min the temperature rises slowly to ~ + 20 °C. At this temperature a very exothermic reaction starts, that needs immediate intensive cooling to be controlled. The cooling capacity is adjusted to maintain a gentle reflux. After 10–15 min the reaction ceases and TLC (cyclohexane/toluene 1:1) indicates complete transformation of **11** (R_f = 0.72) to title compound **12** (R_f = 0.45) and polar byproducts. The mixture is poured slowly into ice-cold sat. aq $NaHCO_3$ (1 L) and extracted with Et_2O (3 × 500 mL). The combined extracts are washed with $NaHCO_3$ (2 × 250 mL), brine (100 mL), dried ($MgSO_4$), and the solvent is evaporated. The residue is chromatographed with cyclohexane/toluene 2:1 through silica gel to give the intensively yellow solid **12**; yield: 15.8 g (24%) mp 122–124 °C.

^{1}H-NMR and MS of this compound indicate, that it contains ~ 7% of an impurity with a molecular weight of 344 (additional oxygen atom). ^{1}H-NMR ($CDCl_3$/TMS): δ = 1.15–1.40 (m, 18 H, CH_3), 1.98 (sept, 1 H, CH), 2.63 (sept, 1 H, CH), 3.24 (sept, 1 H, CH), 7.08 (AA'BB', 4 H_{arom}).

MS (DCI, isobutane): m/z (%) = 329 $M + H^+$, 100).

2-(*p*-Fluorophenyl)-3,5,6-triisopropyl-1,4-hydroquinone (13):
The solution of the impure quinone **12** (11.1 g, 33.8 mmol) in abs. EtOH (740 mL) is purged with N_2. Sodium borohydride (6.3 g, 166.5 mmol) is added in portions. The reaction progress is obvious from the decolorization of the originally intensively yellow mixture (usually 1 h). The solvent is removed *in vacuo*, and vacuo is released with argon. To the residue is added slowly with ice-cooling 2 N HCl (500 mL), that had been purged with N_2 before. Et_2O (500 mL) is decanted from $LiAlH_4$ and added to the mixture. The mixture is

shaken, the organic phase is separated, the solvent is evaporated *in vacuo*, and the vacuo is released with argon. The residue is dried under high vacuum. The powder is digerated with pentane. The solid is suction filtered under N_2 and dried *in vacuo* to give **13** as a colorless powder; yield: 9.7 g (87%); mp 195–197°C.

Whereas the solution of **13** is highly sensitive to oxidation (to give **12**, yellow colour), solid **13** is only moderately sensitive.

$C_{21}H_{27}FO_2$	calc.	C 76.33	H 8.24	F 5.75	
(330.4)	found	76.17	8.20	5.61	

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.23 (d, 6H, J = 7.0 Hz, CH_3), 1.34 (d, 6H, J = 7.0 Hz, CH_3), 1.42 (d, 6H, J = 7.0 Hz, CH_3), 2.66 (sept 1H, CH), 3.40–3.70 (s, very broad, restricted rotation of isopropyl, 2H, CH), 4.12 (s, 1H, OH), 4.39 (s, 1H, OH), 7.12–7.28 (m, 4 H_{arom}).

MS (DCI, isobutane): m/z (%) = 330 (M^+, 100).

2-(*p*-Fluorophenyl)-4-thiocyanato-6-isopropylphenol (14):

Sodium thiocyanate (1.680 kg, 20.6 mol, 5.0 equiv.) is added to the solution of 2-(4-fluorophenyl)-6-isopropylphenol (**7a**, 0.947 kg, 4.11 mol, 1.0 equiv.) in MeOH (4.5 L). In another flask Br_2 (317 mL, 0.986 kg, 6.17 mol, 1.5 equiv.) is dissolved with intensive cooling in MeOH (1.0 L). This solution is added dropwise at 10–15°C to the above suspension (1 h). The mixture is stirred for 30 min at ambient temperature. The MeOH is removed *in vacuo* at < 30°C. H_2O (2 L) and toluene (3 L) is added to the residue and the suspension is stirred for 1 h. It is filtered through a G3-glass frit covered with Celite. The Celite is washed with toluene (1 L). The combined toluene phases are concentrated to dryness *in vacuo* (< 40°C). Cyclohexane (6 L) is added to the residue and the suspension is heated to reflux, leading to dissolution of most of the solid. Charcoal (40 g) is added and reflux is continued for 5 min.

The hot suspension is filtered. The filtrate is seeded with pure crystals of **14** and allowed to stand at 5°C overnight. The crystals are collected, swirled with ice-cold cyclohexane, collected again, and dried *in vacuo* to give **14** (0.981 kg, mp 86–89°C). The combined cyclohexane filtrates are concentrated to give a semisolid (218 g). Petroleum ether (bp 80–90°C, 500 mL) is added and heated to reflux to give a clear solution, that is seeded with crystals of **14**, allowed to cool slowly, and then kept at 0°C overnight. The crystals are collected to give **14** (98 g). This crop is recrystallized from petroleum ether again, to give **14** (87.3 g, mp 88–91°C). Total yield: 1.068 g (91%). This compound is > 97% pure by ^{1}H-NMR, but the crystals are slightly yellow.

An analytically pure sample is obtained by an additional recrystallization from hot cyclohexane/charcoal to give colorless crystals, mp 95–96°C.

$C_{16}H_{14}FNOS$	calc.	C 66.88	H 4.91	F 6.61	N 4.87	S 11.16
(287.4)	found	66.75	5.00	6.53	4.78	11.02

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.26 (d, 6H, J = 7.0 Hz, CH_3), 3.32 (sept, 1H, CH), 5.46 (s, 1H, OH), 7.0–7.6 (m, 6 H_{arom}).

MS (DCI, isobutane): m/z (%) = 288 ($M + H^+$, 100), 287 (M^+, 30), 272 ($M^+ - CH_3$, 10), 261 ($M^+ - CN$, 26).

2-(*p*-Fluorophenyl)-6-isopropyl-4-mercaptophenol (15):

The solution of the thiocyanate **14** (32.5 g, 113 mmol) in THF (150 mL) is added dropwise to the suspension of $LiAlH_4$ (7.5 g, 198 mmol) in THF (20 mL). The mixture is refluxed for 90 min under N_2. TLC (cyclohexane/EtOAc 9:1) indicates complete reaction of the thiocyanate **14** (R_f = 0.16) to the thiol **15** (R_f = 0.26). Care is taken during workup, to expose the product to as little oxygen contact as possible, because it is subject to easy oxidative dimerization to give the corresponding disulfide. When conc. HCl (100 mL) is added dropwise with cooling, the aluminum salts dissolve. The solution is extracted with degassed Et_2O (3 × 200 mL). The extracts are washed with brine (100 mL), dried ($MgSO_4$) and the solvent is removed in vacuo. The residue is filtered with cyclohexane/EtOAc 9:1 under N_2-pressure through silica gel to give a colorless oil; yield: 27.3 g (92%)

$C_{15}H_{15}FOS$	calc.	C 68.67	H 5.76	F 7.24	S 12.22	
(262.3)	found	68.48	5.89	7.08	12.01	

IR ($CHCl_3$): ν = 3555 (OH), 2560 (weak, SH), 1510, 1455, 1223, 840 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.27 (d, 6H, J = 7.0 Hz, CH_3), 3.30 (sept, 1H, CH), 3.40 (s, 1H, SH), 5.06 (s, 1H, OH), 6.93–7.63 (m, 6 H_{arom}).

MS (DCI, isobutane): m/z (%) = 262 (M^+, 100), 247 ($M^+ - CH_3$, 28).

2,2-Bis[3-(*p*-fluorophenyl)-4-hydroxy-5-isopropylphenylthio]propane (16):

The mercaptophenol **15** (27.3 g, 104 mmol) is dissolved in benzene (100 mL), that has been purged with N_2 before. 2,2-Dimethoxypropane (16 mL, 13.5 g, 130 mmol) is added, followed by TsOH · H_2O (~ 100 mg, ~ 0.5 mmol). The reaction mixture is stirred for 30 min at 25°C, 8 h at reflux. It is washed with aq NaOAc solution (100 mL), then with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil (29.0 g) is chromatographed with cyclohexane/toluene (1:1 + 0.1% NEt_3) through silica gel to give a yellow oil (26.0 g, 89%), that crystallizes on cooling, mp 20–25°C.

$C_{33}H_{34}F_2O_2S_2$	calc.	C 70.18	H 6.07	F 6.73	S 11.36	
(564.8)	found	70.04	6.18	6.57	11.26	

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.28 (d, 12H, J = 7.0 Hz, aryl-$C(CH_3)_2$), 1.53 (s, 6H, $SC(CH_3)_2S$), 3.32 (sept, 2H, CH), 5.26 (s, 2H, OH), 7.0–7.7 (m, 12 H_{arom}).

MS (FAB, 3-NBA/LiI): m/z (%) = 571 ($M + Li^+$, 5), 522 ($M^+ - C_3H_6$, 3), 304 (62), 303 (100).

MS (DCI, isobutane): m/z (%) = 303 (M^+ – (2-*p*-fluorophenyl-4-thiyl-6-isopropylphenol), 100).

2-*p*-Fluorophenyl-4-*p*-fluorophenylthio-6-isopropylphenol (21):

A THF-solution of *p*-fluorophenylmagnesium bromide is prepared as described (Method A) from 1-bromo-4-fluorobenzene (22.0 g, 126 mmol) and magnesium turnings (3.11 g, 128 mmol) in dry THF (100 mL).

A solution of thiocyanate **14** (6.04 g, 21 mmol) in THF (50 mL) is added dropwise at 50°C, and the reaction mixture is stirred for 2 h at 40–50°C. It is poured into ice-cold 2N HCl (500 mL) and extracted with Et_2O (3 × 200 mL). The combined extracts are washed with brine (100 mL), dried ($MgSO_4$), and the solvent is removed *in vacuo*. The residual colorless oil (7.5 g, 100%) is pure according to TLC (cyclohexane/EtOAc 9:1, R_f = 0.35), ^{1}H-NMR and MS. It can be distilled (bp 192–193°C/0.7 mbar) or chromatographed (recovery 96%).

$C_{21}H_{18}F_2OS$	calc.	C 70.77	H 5.09	F 10.66	S 9.00	
(356.4)	found	70.73	5.27	10.54	8.81	

^{1}H-NMR ($CDCl_3$): δ = 1.25 (d, 6H, J = 7.0 Hz, CH_3), 3.31 (sept, 1H, CH), 5.22 (s, 1H, OH), 6.8–7.8 (m, 10 H_{arom}).

MS (DCI, isobutane): m/z (%) = 357 ($M + H^+$, 72), 356 (M^+, 100).

2-Bromo-6-isopropyl-4-thiocyanatophenol (17):

Crude 2-isopropyl-4-thiocyanatophenol is obtained from *o*-isopropylphenol in analogy to the procedure given for **14**.

Iron powder (500 mg) is added to the solution of crude 2-isopropyl-4-thiocyanatophenol (109 g, 564 mmol) in CCl_4 (1 L). At 15–20°C with intensive stirring Br_2 (94.6 g, 592 mmol) is added dropwise during 30 min. The mixture is stirred at 20°C for 30 min, then divided between CH_2Cl_2 (1 L) and 10% aq $Na_2S_2O_3$ (500 mL). The organic phase is washed again with $Na_2S_2O_3$ (250 mL), then with brine (250 mL), dried ($MgSO_4$), and the solvent is evaporated in vacuo. The residue is chromatographed through silica gel with cyclohexane/toluene 1:1 to give **17** as a colorless oil, that slowly crystallizes; yield: 62.0 g (40% from 2-isopropyl-4-thiocyanatophenol); mp 44–45°C.

$C_{10}H_{10}BrNOS$	calc.	C 44.13	H 3.70	Br 29.36	N 5.15	S 11.78	
(272.1)	found	43.97	3.86	29.15	5.11	11.64	

^{1}H-NMR ($CDCl_3$): δ = 1.25 (d, 6H, J = 7.0 Hz, CH_3), 3.32 (sept, 1H, CH), 5.86 (s, 1H, OH), 7.35 (d, 1 H_{arom}, J = 2.4 Hz), 7.59 (d, 1 H_{arom}, J = 2.4 Hz).

MS (DCI, isobutane): m/z (%) = 272/274 ($M + H^+$, 100), 271/273 (M^+, 48), 256/258 ($M^+ - CH_3$, 16).

2-Bromo-4-*p*-fluorophenylthio-6-isopropylphenol (18):
In an attempt to transform **17** directly to **21**, it is reacted with *p*-fluorophenylmagnesiumbromide (6 equiv.) in the presence of catalytic $(PPh_3)_4Pd$. A solution of thiocyanate **17** (1.1 g, 4.0 mmol) in THF (20 mL) is purged with N_2. $(PPh_3)_4Pd$ (462 mg, 0.4 mmol) is added. The solution is stirred for 10 min and a solution of the Grignard reagent (24.0 mmol) in THF (15 mL) is added at once. The mixture is refluxed (3 h), then divided between 2N HCl (50 mL) and Et_2O (100 mL). The organic phase is washed with sat. $NaHCO_3$ (50 mL), brine (25 mL), dried ($MgSO_4$), and the solvent is evaporated to give an oil, that is chromatographed through silica gel with cyclohexane/EtOAc (50:1) to give a colorless solid (1.16 g, 85%).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.23 (d, 6H, J = 7.0 Hz, CH_3), 3.28 (sept, 1H, CH), 5.63 (s, 1H, OH), 6.88 (d, 1 H_{arom}, J = 9.6 Hz), 7.06–7.23 (m, 5 H_{arom}).

MS (DCI, isobutane): m/z (%) = 341/343 ($M + H^+$, 42), 340/342 (M^+, 100), 325/327 ($M^+ - CH_3$, 9).

1-Benzyloxy-4-(*p*-fluorophenylthio)-2-isopropylbenzene (20):
1-Benzyloxy-2-bromo-4-*p*-fluorophenylthio-6-isopropylbenzene (prepared from **18** in analogy to the procedure given for **2**, colorless oil, yield 87% after silica gel chromatography with cyclohexane/toluene 10:1) cannot be transformed to its Grignard reagent **19** in analogy to the procedure given for **3**, method A. The reaction cannot be initiated with the usual starters (etheral CH_3MgI or catalytic 1,2-dibromoethane). In an attempt to prepare **21** via a palladium-catalyzed coupling of **19** with 4-fluoro-1-iodobenzene, **19** is prepared by the entrainment technique[21]: Mg-turnings (5.10 g, 210 mmol) are activated with some iodine crystals, then dry THF (15 mL) is added and the suspension is heated to 50 °C. A solution of 1-benzyloxy-2-bromo-4-*p*-fluorophenylthio-6-isopropylbenzene (45.1 g, 104.6 mmol) and 1,2-dibromoethane (19.7 g, 105 mmol) in THF (50 mL) is added dropwise to maintain a gentle reflux. The mixture is refluxed for one additional hour, leaving only a very small amount of unreacted Mg.

In a second flask the solution of 4-fluoro-1-iodobenzene (23.3 g, 105 mmol) in THF (50 mL) is purged with nitrogen. $(PPh_3)_4Pd$ (2.3 g, 2 mmol) is added. The solution is warmed to 40 °C and the above Grignard solution **19** (40 °C) is added via flex-needle.[19] The mixture is refluxed for 90 min, allowed to cool, and poured into conc. HCl (100 mL)/ice (100 g). The mixture is extracted with Et_2O (3 × 100 mL). The extracts are washed with 2N HCl (100 mL), sat. $NaHCO_3$ (100 mL), brine (50 mL), dried ($MgSO_4$), and the solvent is evaporated. The residual oil is chromatographed with cyclohexane/EtOAc (100:1) through silica gel (2 L) to give **20** as a colorless oil (35.0 g, 95%), that slowly crystallized in the refrigerator at 0 °C.

$C_{22}H_{21}FOS$	calc.	C 74.96	H 6.01	F 5.39	S 9.10
(352.5)	found	74.85	6.18	5.33	8.93

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.22 (d, 6H, J = 7.0 Hz, CH_3), 3.39 (sept, 1H, CH), 5.10 (s, 2H, CH_2), 6.88 (d, 1H, J = 8.8, H_{ortho}), 6.97 (AA'BB', 2 H_{arom}), 7.18–7.28 (m, 3 H_{arom}), 7.31–7.48 (m, 6 H_{arom}).

MS (DCI, isobutane): m/z (%) = 353 ($M + H^+$, 29), 352 (M^+, 19), 91 (100).

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