Design and Preparation of Polyphenyl Distance Markers for Solid-State ^{19}F NMR

KENJI MONDE,[†] YORK TOMITA,[‡] M. LANE GILCHRIST JR.,[¶] ANN E. MCDERMOTT, KOJI NAKANISHI*
Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA

(Received 23 August 2000 and in revised form 11 October 11 2000)

Abstract. With ^{13}C-labeled samples, it is possible to measure internuclear distances up to 7 Å by solid-state NMR, thus providing a powerful tool for probing ligand–receptor interactions. However, limitations in measurable distances and appreciable natural abundant ^{13}C background signals present problems in solid-state ^{13}C NMR. In order to overcome these disadvantages, a set of reference compounds with known F–F distances, namely, quinolinol, *p*-biphenyl, and *p*-terphenyl-bearing trifluoromethyl and trifluoromethylthio groups, have been synthesized. The preparation of these reference compounds and means for diluting these references in solid-state NMR are described.

INTRODUCTION

Magnetization exchange mediated by dipolar coupling has been used for determining internuclear distances in molecules in the solid state.[1–3] In the case of ^{13}C-labeled samples, it is possible to measure internuclear distances up to 7 Å by solid-state NMR.[2,3] Various pulse sequences have been developed for distance measurements; some of the widely used techniques based on homonuclear dipolar interactions being rotational resonance[4] and radio-frequency-driven dipolar recoupling.[5] Distance measurements of a doubly ^{13}C-labeled retinal bound to bacteriorhodopsin[6] have demonstrated the utility of solid-state NMR as a powerful tool for probing ligand–receptor interactions. However, limitations in measurable distances and appreciable natural abundant ^{13}C background signals present problems in solid-state ^{13}C NMR.

To overcome these disadvantages, we have recently conducted solid-state ^{19}F NMR distance measurements.[7] Since fluorine has a larger gyromagnetic ratio than that of ^{13}C by a factor of 3.7, longer distance measurements can be obtained with enhanced sensitivity. Moreover, fluorine can be readily incorporated into ligand molecules by synthesis or biosynthesis. Other attributes of the fluorine nuclei are the large chemical shift anisotropy and, unlike carbon and hydrogen, the absence of NMR background signals in nature. In order to measure long-range ^{19}F–^{19}F internuclear distances in biological systems, we have examined the magnetization exchange effects between two fluorine functional groups using distance marker compounds in the range of 5–16 Å. The results have shown that distances up to ca. 12 Å can be measured.[7] In the following, we describe the design and preparation of polyphenyl compounds bearing two fluorine functional groups that were used as distance markers. These series of molecules (nicknamed "shishkebabs" from the molecular shape) fulfilled the requirements for solid-state ^{19}F NMR measurements.

RESULTS AND DISCUSSION

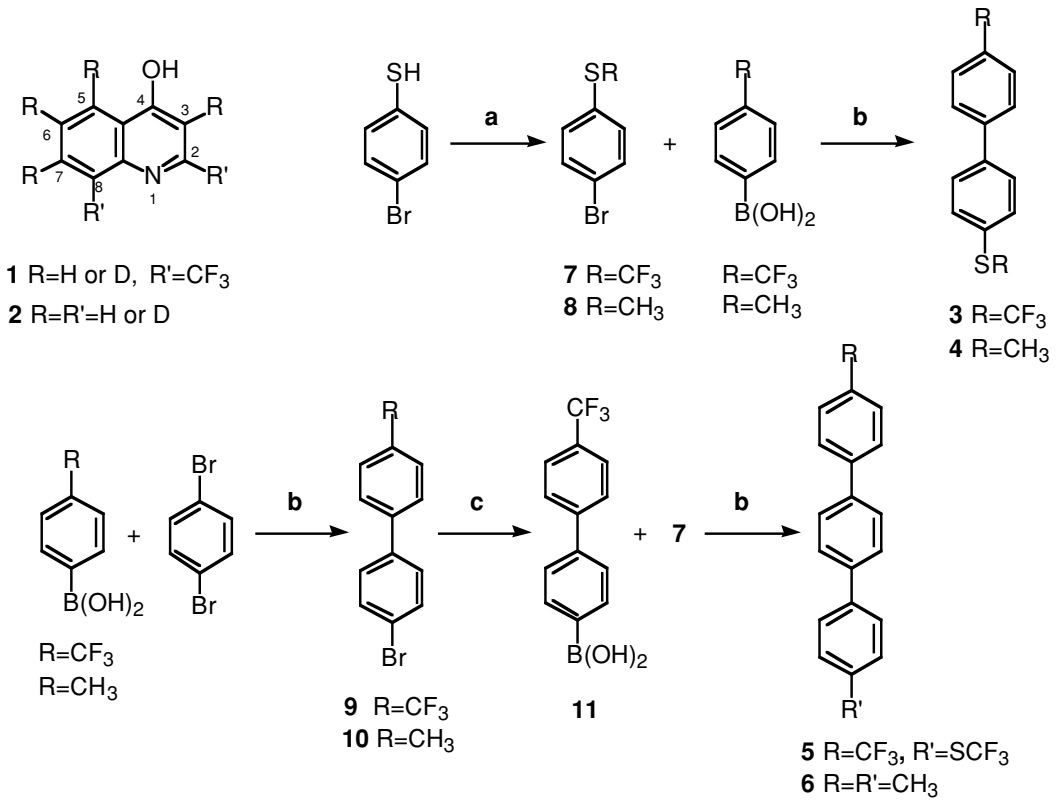
After examination of several fluorine functional groups, e.g., $ArOCF_3$, $ArCD_2F$, and ArF, the trifluoromethyl and trifluoromethylthio groups attached to rigid aromatic ring systems were chosen. These two functionalities satisfy the criteria for solid-state NMR distance measurements since their ^{19}F NMR signals are well separated ($\Delta\delta$ = ca. 20 ppm) and since, compared to mono or

*Author to whom correspondence should be addressed.
E-mail: kn5@columbia.edu
Present addresses: [†]Institute for Chemical Reaction Science, Tohoku University, Katahira 2-1-1, Sendai 980-8577, Japan. [‡]Lombardi Cancer Center, Georgetown University Medical Center, 3970 Reservoir Road, NW, Washington, DC 20007, USA. [¶]Department of Chemical Engineering, City College of New York, 140th St. and Convent Ave., New York, NY 10031, USA.

Table 1
Perdeuteration of compounds **1** and **2**

		conditions				deuteration ratio (%)[a]					
entry	substrate	reagents	time	method[b]	yield	2	3	5	6	7	8
1	**1**	concd D_2SO_4	11 h	A	17%		0	0	0	0	
2	**1**	3M D_2SO_4–D_2O–DME	4 h	A	99%		99	0	0	0	
3	**1**	40% NaOD–D_2O	15 min	B	85%		50	0	0	0	
4	**1**	10% NaOD–D_2O	5 min	B	37%		61	0	33	71	
5	**1**	8% NaOD–D_2O	10 min	B	24%		70	0	45	78	
6	**1**	8–10% NaOD–D_2O	9 min × 4[c]	B	3%		78	27	51	83	
7	**2**	concd D_2SO_4	5 h	A	45%	0	99	99	99	0	99
8	**2**	37% DCl–D_2O	15 min	B	29%	0	99	0	0	0	0
9	**2**	concd D_2SO_4	25 min	B	decomp						
10	**2**	40% NaOD–D_2O	20 min	B	33%	99	99	50	99	99	99
11	**2**	10–40% NaOD–D_2O	10 min × 4[c]	B	21%	98	98	55	85	89	92

[a] Numbers denote deuteration sites on the quinoline ring system (see Scheme 1). [b] Method A: Mixture was heated in sealed tubes at 150~200 °C. Method B: Mixture was heated in a Teflon bomb in the microwave oven. [c] Mixture was submitted to four microwave treatments.



Scheme 1. Synthesis of polyphenyl distance markers and dilutants. (a) CF_3I, Et_3N/DMF; (b) $Pd(PPh_3)_4$/20% Na_2CO_3–H_2O–toluene; (c) i) *n*-BuLi/THF, ii) $B(O\text{-}i\text{-}Pr)_3$, iii) 10% HCl.

difluoro functional groups, the trifluoromethyl groups have moderate spin lattice relaxation times with strong intensity. The perdeuterated derivative of the commercially available 2,8-bis(trifluoromethyl)-4-quinolinol **1** was used as the model with a short F–F distance. As references for longer F–F distances, the series *p*-biphenyl **3**, *p*-terphenyl **5**, and *p*-quaterphenyl[8] compounds bearing trifluoromethyl and trifluoromethylthio groups at terminal positions were employed. The interfluorine distances in these rigid molecules are 5.4 Å for **1**, 11.5 Å for **3**, 15.8 Å for **5**, and 20.1 Å for the *p*-quaterphenyl compound, as estimated by Macromolecule 5.0.

Biphenyl and terphenyl fluorinated compounds **3**, **5** were synthesized mainly by sequential Suzuki coupling reactions.[9] Trifluoromethylation of 4-bromothiophenol was performed by trifluoromethyl iodide in the presence of triethylamine.[10] The resulting bromothioanisole **7** was subjected to cross coupling reaction with 4-trifluoromethylphenylboronic acid, with $Pd(PPh_3)_4$ as catalyst, to give the biphenyl compound **3**. Terphenyl compound **5** was prepared by sequential coupling. Namely, coupling of trifluoromethylphenylboronic acid with excess 1,4-dibromobenzene gave mono coupling compound **9**, 74% yield. This was subjected to metal-halogen exchange followed by a triisopropyl borate-hydrolysis protocol[11] to afford **11**, which, upon cross coupling with **7**, yielded the terphenyl compound **5**, 82% yield.

To measure the distances correctly between the two groups in these molecules, intermolecular dipolar couplings from neighboring fluorine compounds should be minimized. For this purpose, several methods were examined, including host–guest techniques using organic or inorganic host molecules. Finally, it was found that dilution by co-crystallization with structurally similar nonfluorinated compounds was the most effective method. Since the nonfluorinated molecules, so-called "dilutants", should be structurally similar to the corresponding fluorinated molecules, compounds **2**, **4**, and **6**[12] were designed for **1**, **3**, and **5**, respectively. Single Suzuki coupling of 4-bromothioanisole **8** with 4-methylphenylboronic acid gave the biphenyl dilutant **4**. Synthesis of terphenyl **6** was performed by stepwise coupling reactions. Excess of 1,4-dibromobenzene was reacted with 4-methylphenylboronic acid to give 4-bromo-4′-methylbiphenyl **10** in 87% yield. The second coupling reaction of **10** with boronic acid gave terphenyl dilutant **6** as a white solid. Careful crystallization of the nonfluorinated compound with trace amounts of the fluorinated sample from moderate solvents at ambient temperature gave samples for solid-state NMR measurements. In some cases, lyophilization of frozen benzene containing the dilutant and a small amount of the fluorine sample was performed. The ratio of fluorinated compounds to nonfluorinated compounds, which was <1%, was determined by HPLC.

Perdeuterio-**1** and -**2** were prepared in order to minimize the effects of proton coupling and to compare with magnetization exchange experiments obtained from the fully protonated samples. Perdeuteration of **1** and **2** was achieved by base-catalyzed deuterium–hydrogen exchange reaction in a microwave oven.[13] Microwave irradiation accelerated the deuterium exchange rate of **1** and **2**, especially under basic conditions (Table 1). Almost complete exchange was observed by sequential microwave irradiation of both **1** and **2** (Table 1, entries 6 and 11), while high temperature deuterium exchange reaction of **1** (3M D_2SO_4, 200 °C) gave only 3-*d*-**1** (Table1, entry 2).

The present study describes the preparation of polyphenyl distance marker compounds, including the dilution methods best suited for solid-state ^{19}F NMR. Due to the synthetic ease of these compounds, they are suited for use as references for calibration of distance measurements in organic host–guest systems or in macromolecular biological systems. Details of the solid-state ^{19}F NMR studies will be published elsewhere.[7]

EXPERIMENTAL SECTION

General

Melting points are uncorrected. ^1H and ^{13}C spectra were measured on Bruker DRX 400 or DMX 300 spectrometers with tetramethylsilane as internal standard. ^{19}F NMR spectra in solution were measured on a Varian VXR 200 spectrometer with fluorobenzene as the external standard. IR spectra were recorded on a Perkin-Elmer Paragon 1000FT IR spectrophotometer as $CHCl_3$ solution or KBr pellets. Measurements of low- and high-resolution mass spectra were performed on a NERMAG R10-10 or a JEOL JMS-DX 303HF mass spectrometer. UV spectra were recorded on a Perkin-Elmer Lambda 40 UV spectrometer. HPLC analysis was performed with a Perkin-Elmer Model Series 4 liquid chromatograph with YMC-Pack SIL (150 × 4.6 mm i.d., S-3 µm, 120 Å) with hexane. Microwave reactions were conducted in a commercially available Sanyo-EM729 microwave oven (900 W). Analytical TLC was performed with precoated silica gel plates (Merck Art 7754) and preparative TLC with Analtech Uniplate silica gel GF preparative layers, 20 × 20 cm (1000 microns). Silica gel used for flash column chromatography was Selecto Scientific silica gel, 32–63 mesh (Art 162824).

Synthesis

Perdeuterio-2,8-bis(trifluoromethyl)-4-quinolinol ***(1)***. Compound **1** (360 mg, 1.28 mmol) was dissolved in 12 mL of 10% NaOD–D_2O, poured into Teflon bombs (2 mL × 6) which were then placed in the center of the microwave oven. The high energy setting was used three times for 3 min each time. The combined aqueous reaction mixture was diluted with water (200 mL) and acidified with 6 M HCl to pH ~1. To the acidic aqueous solution, solid $NaHCO_3$ was added gradually, and the mixture was extracted twice with ethyl acetate (200 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give first residue (174 mg, 48%). The residue was submitted to a second heating in the same manner and workup. Microwave heating was performed a total of three times to obtain perdeuterated **1** (10 mg, total 3%). Further purification by PTLC (SiO_2, benzene/ethyl acetate) gave pure perdeuterated **1** (3.5 mg). Deuteration ratio was determined by ^1H NMR comparison to a phenolic signal as an internal standard. Non-labeled com-

pound: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.37 (s, 1H, 3-H), 7.83 (dd, J = 8.4, 7.3 Hz, 1H, 6-H), 8.28 (d, J = 7.3 Hz, 1H, 7-H), 8.59 (d, J = 8.4 Hz, 1H, 5-H), 11.40 (brs, 1H, OH). Labeled compound: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.37 (0.22H), 7.83 (0.49H), 8.28 (0.17H), 8.59 (0.73H), 11.20 (brs, 1H, OH).

Perdeuterio-4-hydroxyquinoline ***(2)***. Compound **2** (550 mg, 3.79 mmol) was dissolved in 18 mL of 10% NaOD–D_2O, poured into Teflon bombs (2 mL × 9), and placed in the center of the microwave oven. The high energy setting was used twice for 5 min each time. The combined aqueous reaction mixture was diluted with water (300 mL) and acidified with 6 M HCl to pH ~1. To the acidic aqueous solution, solid $NaHCO_3$ was added gradually, and the mixture was extracted twice with ethyl acetate (300 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the first residue (416 mg, 76%). The residue was submitted to a second heating in the same manner and workup. A total of four microwave heatings were performed to give perdeuterio-**2** (117 mg, total 21%). Deuteration ratio was determined by ^{1}H NMR comparison to a phenolic signal as internal standard. Non-labeled compound: ^{1}H NMR (400 MHz, acetone-d_6) δ 6.06 (d, J = 7.5 Hz, 1H, H-3), 7.30 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H, 6-H), 7.55 (d, J = 7.8 Hz, 1H, 8-H), 7.61 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H , 7-H), 7.85 (d, J = 7.5 Hz, 1H, 2-H), 8.20 (dd, J = 8.1, 1.1 Hz, 1H, 5-H), 10.75 (brs, 1H, OH). Labeled compound: ^{1}H NMR (400 MHz, acetone-d_6) δ 6.06 (0.02H), 7.30 (0.15H), 7.55 (0.08H), 7.61 (0.11H), 7.85 (0.02H), 8.20 (0.45H), 10.65 (brs, 1H, OH).

4-Trifluoromethyl-4′-trifluoromethylthiobiphenyl ***(3)***. To a solution of **7** (56 mg, 0.22 mmol) and $Pd(PPh_3)_4$ (76 mg, 0.066 mmol) in a 20% Na_2CO_3 aqueous solution (4 mL) and toluene (4 mL) under argon atmosphere and with stirring at room temperature, was added 4-trifluromomethylphenylboronic acid (52 mg, 0.27 mmol). The mixture was refluxed for 2 h under vigorous stirring. The reaction mixture was then diluted with water and extracted with ether. The combined ether solution was washed with water, then dried over Na_2SO_4. The residue obtained after solvent removal in vacuo was submitted to silica gel flash column chromatography (pentane) to give a white solid (65 mg, 92%): mp 38–39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.1 (q, J_{CF} = 270 Hz, C), 124.4 (brs, C), 126.0 (CH), 127.6 (CH), 128.3 (CH), 129.6 (q, J_{CF} = 307 Hz, C), 130.3 (q, J_{CF} = 33 Hz, C), 136.8 (CH), 142.3 (C), 143.2 (C); ^{19}F NMR (188 MHz, $CDCl_3$) δ –43.0, –63.0; IR ($CHCl_3$) 1392, 1326, 1167, 1130, 1090, 1071, 1007, 825 cm^{-1}; UV (CH_3CN) λ_{max} 262 (ε 22,100), 201 (31,100) nm; MS (EI) m/z 322 (M^+), 253 (M^+–CF_3); HRMS (EI) calcd for $C_{14}H_8F_6S$: 322.0251, found: 322.0259.

4-Bromo-4′-trifluoromethylbiphenyl ***(9)***. To a solution of 1,4-dibromobenzene (1480 mg, 6.25 mmol) and $Pd(PPh_3)_4$ (423 mg, 0.366 mmol) in 20% Na_2CO_3 aqueous solution (8 mL), toluene (15 mL), and dimethoxyethane (DME, 10 mL) was added 4-trifluoromethylphenylboronic acid (232 mg, 1.22 mmol) under argon with stirring at rt. The mixture was refluxed for 6 h under vigorous stirring. The residual boronic acid was oxidized by 30% H_2O_2 (0.5 mL) at rt for 3 h. The reaction mixture was then diluted with water and extracted twice with ether. The combined ether solution was washed with water and dried over Na_2SO_4. The residue obtained after solvent removal in vacuo was submitted to flash chromatography on silica gel (pentane) to give a white solid (272 mg, 74%): mp 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (brd, J = 8.4 ± 0.3 Hz, 2H), 7.60 (brd, J = 8.4 ± 0.3 Hz, 2H), 7.65 (brd, J 8.4 ± 0.3 Hz, 2H), 7.70 (brd, J = 8.4 ± 0.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 122.6 (C), 124.2 (q, J_{CF} = 271 Hz, C), 125.8 (brs, CH), 127.2 (CH), 128.8 (CH), 129.7 (q, J_{CF} = 32 Hz, C), 132.1 (CH), 138.6 (C), 143.4 (C); ^{19}F NMR (188 MHz, $CDCl_3$) δ –62.4; IR ($CHCl_3$) 1389, 1326, 1169, 1130, 1072, 1020, 1005, 854, 819 cm^{-1}; UV (CH_3CN) λ_{max} 260 (ε 22,900), 206 (31,800) nm; MS (EI) m/z 302 (M^+), 300 (M^+), 201, 152; HRMS (EI) calcd for $C_{13}H_8BrF_3$: 299.9762, found: 299.9766.

4′-Trifluoromethyl-4-biphenylboronic acid ***(11)***. To a solution of bromide **9** (112 mg, 0.372 mmol) in dry THF (4 mL) in argon at –78 °C, was added 1.6 M *n*-BuLi hexane solution (256 µL, 0.410 mmol). The pale yellow reaction mixture was kept at –78 °C for 20 min and treated with (i-PrO)$_3$B (172 µL, 0.744 mmol) at –78 °C, and gradually warmed to rt. After 1 h, water (1 mL) and then 10% aqueous HCl (5 mL) was added and stirred vigorously for 1 h at rt. The THF was evaporated, and the residual mixture was diluted with water and extracted twice with ether. The combined ether solution was washed with water and dried over Na_2SO_4. The residue was filtered, and the solid was washed with hexane to give almost pure borate (79 mg, 80%). The borate was used for the next coupling without further purification: mp 266–268 °C (dec.); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.72 (brd, J = 8.1 ± 0.3 Hz, 2H), 7.80 (brd, J = 8.1 ± 0.3 Hz, 2H) 7.92 (brd, J = 8.1 ± 0.3 Hz, 2H), 8.00 (brd, J = 8.1 ± 0.3 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 116.8 (C), 125.3 (q, J_{CF} = 271 Hz, C), 126.5 (brs, CH), 127.1 (CH), 128.4 (CH), 130.4 (q, J_{CF} = 34 Hz, C), 135.7 (CH), 141.7 (C), 145.7 (C); ^{19}F-NMR (188 MHz, acetone-d_6) δ –61.2; IR ($CHCl_3$) 3659, 3367, 3019, 1608, 1421, 1409, 1377, 1344, 1324, 1219, 1169, 1129, 1112, 1071, 1006, 825 cm^{-1}; UV (CH_3CN) λ_{max} 261 (ε 22,700), 207 (sh, 28,500) nm; MS (EI) m/z 266 (M^+), 265 (M^+–H), 248 (M^+–H_2O), 222 (M^+–BO_2H), 201, 152; HRMS (EI) calcd for $C_{13}H_{10}BF_3O_2$: 266.0726, found: 266.0732.

4-Trifluoromethyl-4′-trifluoromethylthio-p-*terphenyl* ***(5)***. To a solution of bromide **7** (64 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (57 mg, 0.050 mmol) in 20% Na_2CO_3 aqueous solution (2 mL), toluene (3 mL) and DME (2 mL), was added boronic acid **11** (44 mg, 0.17 mmol) under argon with stirring at rt. The mixture was refluxed for 3 h under vigorous stirring, diluted with water, and extracted twice with ether. The combined ether solution was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (hexane) of the residue gave a white solid (54 mg, 82%): mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.5 (brs, C), 124.3 (q, J_{CF} = 270 Hz, C), 125.8 (d, J_{CF} = 4.1 Hz, CH), 127.3 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 129.6 (q, J_{CF} = 306 Hz, C), 129.7 (q, J_{CF} = 32 Hz, C), 136.8 (CH), 139.5 (C), 143.0 (C),

143.9 (C); ^{19}F NMR (188 MHz, $CDCl_3$) δ –42.6, –62.4; IR ($CHCl_3$) 1388, 1326, 1166, 1120, 1088, 1071, 1006, 819 cm^{-1}; UV (CH_3CN) λ_{max} 289 (ε 40,700), 204 (50,000) nm; MS (EI) *m*/*z* 398 (M^+), 329 (M^+–CF_3); HRMS (EI) calcd for $C_{20}H_{12}F_6S$: 398.0564, found: 398.0553.

4-Methyl-4′-methylthiobiphenyl ***(4)***. To a solution of 4-bromothioanisole (503 mg, 2.48 mmol) and $Pd(PPh_3)_4$ (860 mg, 0.744 mmol) in 20% Na_2CO_3 aqueous solution (20 mL) and toluene (20 mL), was added 4-methylphenylboronic acid (388 mg, 2.85 mmol) under argon with stirring at rt. The mixture was refluxed for 12 h with vigorous stirring, diluted with water, and extracted twice with ether. The combined ether solution was washed with water, and dried over Na_2SO_4. The residue obtained after solvent removal in vacuo was submitted to flash chromatography on silica gel (hexane/*i*-PrOH) to give a white solid (324 mg, 61%): mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.51 (brs, 3H), 7.23 (brd, *J* = 8.1 ± 0.3 Hz, 2H), 7.31 (brd, *J* = 8.1 ± 0.3 Hz, 2H) 7.46 (brd, *J* = 8.1 ± 0.3 Hz, 2H), 7.50 (brd, *J* = 8.1 ± 0.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.6 (CH), 127.0 (CH), 127.2 (CH), 129.5 (CH), 136.9 (C), 137.1 (C), 137.6 (C), 138.0 (C); IR ($CHCl_3$): 3007, 2925, 2864, 1490, 1483, 1440, 1396, 1099, 1004, 968, 840, 807 cm^{-1}; UV (CH_3CN) λ_{max} 283 (ε 24,900), 202 (39,000) nm; MS (EI) *m*/*z* 214 (M^+), 199 (M^+–CH_3); HRMS (EI) calcd for $C_{14}H_{14}S$: 214.0816, found: 214.0807.

4-Bromo-4′-methylbiphenyl ***(10)***.[14] To a solution of 1,4-dibromobenzene (11440 mg, 48.5 mmol) and $Pd(PPh_3)_4$ (230 mg, 0.200 mmol) in 20% Na_2CO_3 aqueous solution (20 mL) and DME (30 mL), was added 4-methylphenylboronic acid (2196 mg, 16.2 mmol) under argon atmosphere with stirring at rt. The mixture was refluxed for 8 h under vigorous stirring. The reaction mixture was then diluted with water and extracted twice with ether. The combined ether solution was washed with water and dried over Na_2SO_4. The residue obtained after solvent removal in vacuo was submitted to flash chromatography on silica gel (pentane) to give a white solid (3488 mg, 87%): mp 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.23 (brd, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 121.1 (C), 126.7 (CH), 128.5 (CH), 129.6 (CH), 131.8 (CH), 137.1 (C), 137.5 (C), 140.0 (C); IR (KBr) 3026, 2919, 1481, 1391, 1312, 1188, 1103, 1072, 1003, 843, 808, 723 cm^{-1}; UV (CH_3CN) λ_{max} 260 (ε 24,700), 200 (47,600) nm; MS (EI) *m*/*z* 248 (M^+), 246 (M^+), 167, 165, 152; HRMS (EI) calcd for $C_{13}H_{11}Br$: 246.0044, found: 246.0047.

4,4″-Dimethyl-p-*terphenyl* ***(6)***.[15] The following protocol differs somewhat from the published method. To a solution of **10** (523 mg, 2.11 mmol) and $Pd(PPh_3)_4$ (227 mg, 0.197 mmol) in 20% Na_2CO_3 aqueous solution (20 mL) and benzene (30 mL), was added 4-methylphenylboronic acid (321 mg, 2.36 mmol) under argon atmosphere with stirring at room temperature. The mixture was refluxed for 18 h under vigorous stirring, diluted with water, and washed with hexane and dichloromethane. The insoluble white solid was filtered and dissolved in dichloromethane with ultrasonication. The dichloromethane solution was washed with water and dried over Na_2SO_4. The residue obtained after solvent removal in vacuo was reprecipitated in chloroform to give a white solid (265 mg, 49%): mp 225–227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 6H), 7.27 (d, *J* = 8.0 Hz, 4H), 7.54 (d, *J* = 8.0 Hz, 4H), 7.65 (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 126.8 (CH), 127.2 (CH), 129.5 (CH), 137.1 (C), 137.9 (C), 139.7 (C); IR ($CHCl_3$) 3030, 2919, 1492, 1391, 1187, 1115, 1004, 971, 858, 826, 809, 739 cm^{-1}; UV (CH_3CN) λ_{max} 284 (ε 41,000), 207 (60,900) nm; MS (EI) *m*/*z* 258 (M^+), 257, 241, 215, 165, 152, 129, 128.

Dilution Method of Fluorine Compounds

2,8-Bis(trifluoromethyl)-4-quinolinol (1)/4-Hydroxyquinoline ***(2)***. (i) Compound **1** was diluted with **2** more than ten times and dissolved in ether or hexane. The solution was warmed in a water bath with stirring to dissolve the compounds completely. The solution was cooled to rt to yield white crystals, which were analyzed by NMR or HPLC to determine the ratio. (ii) Perdeuterated **1** (10 mg) was dissolved into 4 mL of D_2O and heated to 65 °C. The undissolved crystals were solubilized by adding a small amount of acetone. The solution was mixed with 100 mg of perdeuterated **2** and then treated with 10 mL of acetone. After filtration of the small amount of undissolved material, slow removal of solvent gave a white powder.

4-Trifluoromethyl-4′-trifluoromethylthiobiphenyl (3)/4-Methyl-4′-methylthiobiphenyl ***(4)***. Approximately 0.6% of **3** was added to **4** in hot ether. The ether solution was flashed by argon to remove part of ether and the solution was chilled until appearance of first crystals. The resulting crystals were filtered and washed with cold hexane and ether. The sample crystals were analyzed by HPLC to determine the ratio of **3/4** as 0.23%.

4-Trifluoromethyl-4′-trifluoromethylthio-p-*terphenyl (5)/4,4″-dimethyl*-p-*terphenyl* ***(6)***. Compound **5** (0.3 mg) and **6** (104 mg) were dissolved in hot benzene (15 mL). The benzene solution was frozen instantaneously by liquid nitrogen and was lyophilized gradually to give a white powder. HPLC analysis showed **6** contained 0.32% of **5**.

Acknowledgments. This contribution is dedicated in fond memory of our dear friend, Professor Ray Lemieux. The authors gratefully acknowledge the support from the Kanagawa Academy of Science and Technology (KAST) and NIH AI 10187.

REFERENCES AND NOTES

(1) (a) Smith, S.O.; Peersen, O.B. *Annu. Rev. Biophys. Biomol. Struct.* **1992**, *21*, 25–47. (b) Fu, R.; Cross, T.A. *Annu. Rev. Biophys. Biomol. Struct.* **1999**, *28*, 235–268.

(2) Griffin, R.G.; Griffiths, J.M. *Anal. Chim. Acta* **1993**, *283*, 1081–1101.

(3) Peersen, O.B.; Yoshimura, S.; Hoji, H.; Aimoto, S.; Smith, S.O. *J. Am. Chem. Soc.* **1992**, *114*, 4332–4335.

(4) (a) Raleigh, D.P.; Levitt, M.H.; Griffin, R.G. *Chem. Phys. Lett.* **1988**, *146*, 71–76. (b) Levitt, M.H.; Raleigh,

D.P.; Creuzet, F.; Griffin, R.G. *J. Chem. Phys.* **1990**, *92*, 6347–6364.

(5) (a) Bennett, A.E.; Ok, J.H.; Griffin, R.G. *J. Chem. Phys.* **1992**, *96*, 8624–8627. (b) Bennett, A.E.; Rienstra, C.M.; Griffiths, J.M.; Zhen, W.; Lansbury, P.T.; Griffin, R.G. *J. Chem. Phys.* **1998**, *108*, 9463–9479.

(6) (a) Creuzet, F.; McDermott, A.E.; Gebhard, R.; van der Hoef, K.; Spijker-Assink, M.B.; Herzfeld, J.; Lugtenburg, J.; Levitt, M.H.; Griffin, R.G. *Science* **1991**, *251*, 783–786. (b) McDermott, A.E.; Creuzet, F.; Gebhard, R.; van der Hoef, K.; Levitt, M.H.; Herzfeld, J.; Lugtenburg, J.; Griffin, R.G. *Biochemistry* **1994**, *33*, 6129–6136.

(7) Gilchrist, Jr., M.L.; Monde, K.; Tomita, Y.; Iwashita, T.; Nakanishi, K; McDermott, A. *J. Magn. Res.,* in press.

(8) The quarterphenyl compound, 4-trifluoromethyl-4‴-trifluoromethylthio-*p*-quaterphenyl was prepared following the same sequential coupling, but the yield was low due to low solubility in solvents. Solid-state NMR measurements have not been successful with this compound.

(9) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519. (b) Suzuki, A.; Miyaura, N. *Pure Appl. Chem.* **1991**, *63*, 419–422 and references cited therein.

(10) (a) Boiko, V.N.; Shchupak, G.M. *J. Fluorine Chem.* **1994**, *69*, 207–212. (b) Koshechko, V.G.; Kiprianova, L.A.; Fileleeva, L.I.; Rozhkova, Z.Z. *J. Fluorine Chem.* **1995**, *70*, 277–278.

(11) Matteson, D.S. *Tetrahedron* **1989**, *45*, 1859–1885.

(12) Due to the unsuccessful synthesis of 4-methyl-4″-methylthio-*p*-terphenyl, mimic compound **6** was used as the dilutant.

(13) Köves, G.J. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 255–262.

(14) Han, Y.; Walker, S.D.; Young, R.N. *Tetrahedron Lett.* **1996**, *37*, 2703–2706.

(15) Saa, J.M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963–1966.