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The Expedient and Regioselective Metalation of Unprotected Biphenyl-2-, -3-, and -4-carboxylic Acids

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Dedicated to the memory of Subhendu S. Samanta[†]

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Unprotected biphenyl-2-carboxylic acid can be cleanly metalated with *sec*-butyllithium at the position adjacent to the carboxylate and can then be subjected to site-selective electrophilic substitution. The remote C2′-position is attacked by the superbasic mixture of *n*-butyllithium and potassium *tert*-butoxide (LICKOR, 3.5 equiv.) in THF or benzene at 20–60 °C. The resulting dianion cyclizes to give the fluorenone skeleton. The metalation reactions of biphenyl-3- and -4-carboxylic acids are also described.

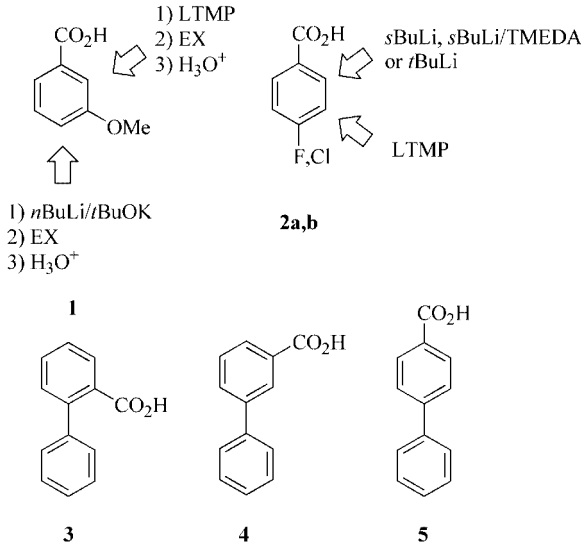
Introduction

Nonpeptidic compounds containing biphenylcarboxylic acid groups inhibit HIV-1 protease, with IC_{50} values of 3.4–74 μM.[1] The structure/inhibitory activity relationship demonstrates the necessity of the biphenylcarboxylic acid group for inhibition. Losartan, one of the most prominent modern antihypertensive drugs, is a (biphenyl-2-yl)tetrazole derivative that antagonizes the angiotensin II AT_1 receptor.[2]

Their importance as precursors of biologically active molecules notwithstanding, very little attention has been paid to the synthesis of biphenyl-2-carboxylic acid derivatives through lithiation reactions. Treatment of tertiary biphenyl-2-carboxamides and biphenyl-2-yloxazolines with LDA or *t*BuLi affords the fluorenone skeleton directly by remote metalation,[3,4] with alkyllithium metalation occurring exclusively *ortho* to the amide group. The carbonyl group is invariably protected prior to metalation

Regioselective lithiation of biphenylcarboxylic acids is a new challenge because of the previously demonstrated *ortho* directing effect of the carboxylic acid group in benzenoid systems.[5,6] In recent work[7] we have reported the metalation of *meta*-anisic acid (**1**) at the doubly activated position by lithium 2,2,6,6-tetramethylpiperidide (LTMP); in contrast, *n*BuLi/*t*BuOK (LICKOR) at low temperature preferentially deprotonates the C4-position.[8]

The metalation of 4-fluoro- and 4-chlorobenzoic acids **2a**, **2b** results in exclusive reaction *ortho* to the carboxylate with *s*BuLi, *s*BuLi/TMEDA, or *t*BuLi, but LTMP selectively metalates the C3-positions.[9] These results corroborate the concept of the achievement of regiocontrol in hy-



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drogen/metal exchange processes through mechanism-based matching of substituents and reagents.[10]

Here we report on the reactivity of biphenyl-2-, -3-, and -4-carboxylic acids **3**–**5** towards sterically hindered lithium amides, alkyllithiums, and LICKOR. The results obtained show that although the CO_2Li group does activate neighboring positions towards metalation, the effect remains relatively weak, enabling regioflexibility since most other electronegative substituents outperform a competing carboxylate group through their superior *ortho*-directing capabilities.

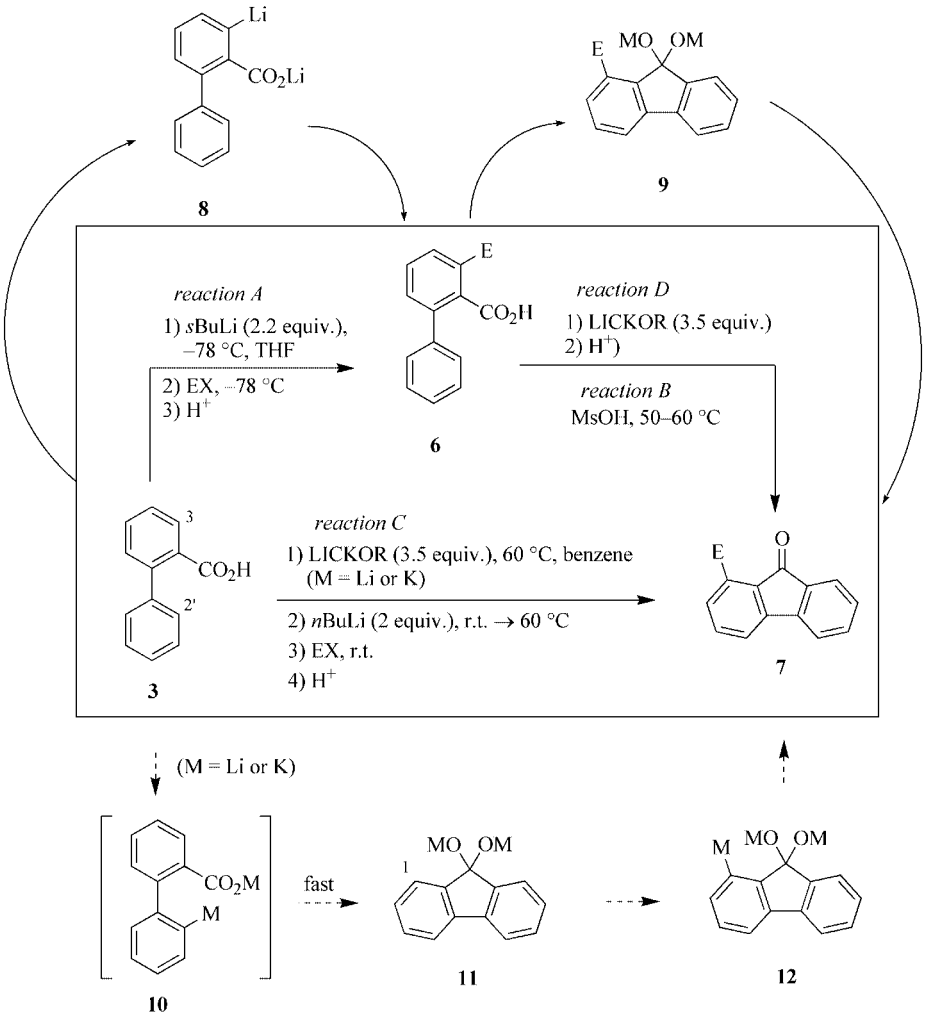
Results and Discussion

Biphenyl-2-carboxylic acid (**3**) undergoes regiospecific metalation *ortho* to the carboxylate substituent (C3) when treated with *sec*-butyllithium (*s*BuLi) in THF at –78 °C (Scheme 1). Trapping of the stable lithium 3-lithiobiphenyl-2-carboxylate (**8**) with a variety of electrophiles (see Table 1) afforded diversely 3-substituted biphenyl-2-carboxylic acids

Table 1. Metalations of biphenyl-2-carboxylic acid (**3**). Preparation of compounds **6** and **7** (Scheme 1).[a]

Cpd.	EX/E	**6** (A)	**7** (B)	**7** (C)	**7** (D)
a	D_2O/D	99[b]	–	70[b]	–
b	MeI/Me	80	95	10	54
c	EtI/Et	63	88	–	58
d	C_2Cl_6/Cl	72	82	30	0
e	$C_2Br_2Cl_4$/Br	71	96	48	–
f	I_2/I	73	92	43	–
g	Me_2S_2/MeS	81	91	49	0
h	Me_3SiCl/Me_3Si	98	0	–	–
i	$n Bu_3Sn$/$n Bu_3Sn$	65[c]	–	–	–
j	DMF/CHO	80[d]	–	–	–
k	PhCHO/PhCH(OH)	93[e]	–	–	–

[a] Yields of recrystallized or chromatographed materials. [b] The isotope ratio was determined by ^{1}H NMR and FIMS: **6a** (reaction A, $1d_0$:$1d_1$ 30:70), **7a** (reaction C, $1d_0$:$1d_1$ 0:100). [c] Recovered as the ester tri-*n*-butyltin 3-(tri-*n*-butylstannyl)biphenyl-2-carboxylate (**6i′**). [d] Compound **6j** was not isolated but was converted directly into 3-hydroxy-7-phenylisobenzofuran-1(3*H*)-one (**14**) by acid treatment upon workup. [e] Compound **6k** was not isolated but was converted directly into 3,7-diphenylisobenzofuran-1(3*H*)-one (**15**) by acid treatment upon workup.



Scheme 1.

6a–k (reaction A).[11] D_2O gave **6a**, in which 70% of the deuterium was incorporated at the carbon C3. Treatment with nBu$_3$SnCl gave the ester **6i′** (68%, Figure 1), which was transformed into *meta*-terphenyl-2′-carboxylic acid (**13**)[12] by the Stille reaction (59%) (Figure 1; see Experimental Section). Acids **6j** and **6k**, the results of treatment of the dianion **8** with DMF and with benzaldehyde, were converted directly into 3-hydroxy-7-phenylisobenzofuran-1(3*H*)-one (**14**) and 3,7-diphenylisobenzofuran-1(3*H*)-one (**15**), respectively, during the acidic workup.

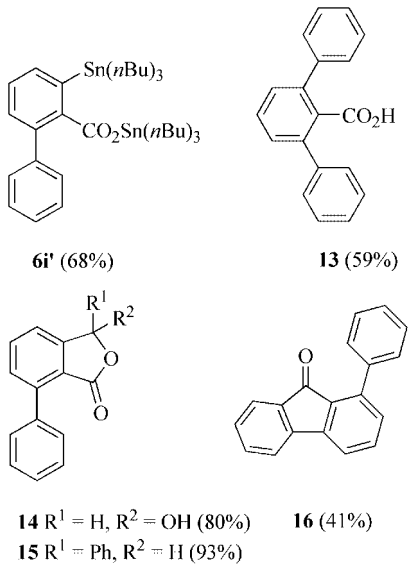


Figure 1. Functionalization of unprotected biphenyl-2-carboxylic acid (**3**).

In this reaction, the alkyllithium presumably approaches the benzoate in the initial step through strong coordination with the highly electron-rich π-system of the carboxylate, producing a pre-lithiation complex [Complex-Induced Proximity Effect (CIPE) process].[13] The directing and accelerating effect of the carboxylate might be due to the stabilization *both* of the initial complex *and* of the transition structure.[14] The coordination by the carboxylate could be stronger in the transition state than in the initial complex;[7] as a result, complexation could increase the rate of reaction by providing a new mechanism with a smaller activation energy (E_a).

Intramolecular Friedel–Crafts acylation by treatment of 3-substituted biphenyl-2-carboxylic acids (**6b–g**) with methanesulfonic acid at 50–60 °C[15] afforded the fluorenones **7b–g** in good yields after column chromatography (reaction B). 1-Phenyl-9*H*-fluoren-9-one (**16**) was prepared from the teraryl carboxylic acid **13** under the same reaction conditions (41%, Figure 1).

In the literature, fluorenones containing aryl substituents at their C1-positions have been prepared either by radical procedures[16] or through fluorenone-1-boronic acid coupling with the corresponding aryl halides.[17] The A + B sequence allows the introduction of a broader range of substituents at the C1-position than is achievable by these methods. The fluorenone skeleton occurs in a wide range of substrates, including marine sediments,[18] kerogen pyrolysates,[19] weathered surface retorted oil shales, and Wilmington petroleum.[20] Fluorenones are also known to function as photoinitiators in various photochemical reactions.[21]

With LICKOR (3.5 equiv.) in THF or benzene at 20–60 °C,[22] biphenyl-2-carboxylic acid (**3**) gave the fluorenone skeleton **7** (E = H; Scheme 1), arising from the metalation of the remote C2′ site (reaction C).[23] The unstable C2′-metalated species **10** has a short lifetime and rapidly cyclizes to give the doubly charged geminal dimetalo dialkoxide group **11**. The equilibrium between the C3-metalated species and the C2′-metalated species is shifted to the right by Le Châtelier's principle. Deuterolysis experiments have shown that both *ortho* (C3) and remote (C2′) positions are metalated under these conditions.[23]

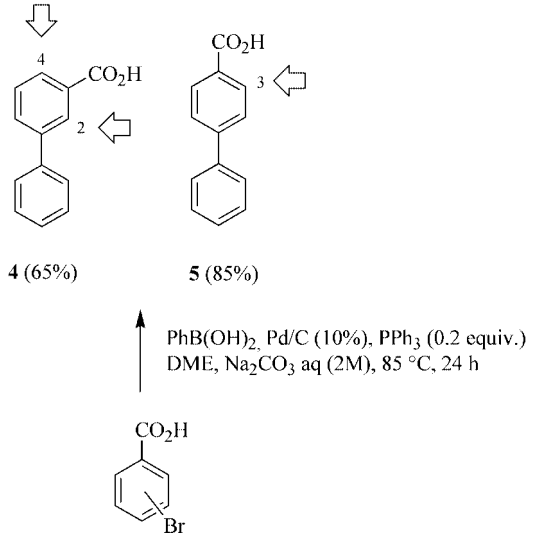
The ^{1}H NMR spectrum of the residue prior to hydrolysis in [D$_8$]THF displays broad signals with poor resolution in the aromatic region, probably due to the presence of aggregates that prevent simple structural elucidation. The dialkoxide **11** is not trappable by electrophiles: treatment with iodomethane or dimethyl sulfate gave the fluorenone **7** even when hydrolysis of the reaction mixture with water was omitted.[23]

When 2 equiv. of nBuLi were added to the mixture composed of **3** and LICKOR (3.5 equiv.) in benzene at 60 °C, quenching with D_2O produced isotopically pure 1-deuterio-9*H*-fluoren-9-one **7a** (E = D, 70%, 100% Id_1). The doubly charged dimetalo dialkoxide group C(OM)$_2$ of **11** presumably directs a second metalation in the adjacent position (C1) to afford the stable 1-metalo-9*H*-fluoren-9,9-dimetalo dialkoxide (**12**), which can be trapped by D_2O after acidic workup. 1-Substituted 9*H*-fluoren-9-ones **7b–k** were obtained successfully with a variety of electrophiles (see Table 1).

1-Substituted 9*H*-fluoren-9-ones (**7**) were also prepared by anionic cyclization of 3-substituted biphenyl-2-carboxylic acids **6**, but results in this case were less satisfactory (reaction D, Scheme 1). Thus, treatment of **6b** or **6c** (R = Me, Et) with LICKOR (3.5 equiv.) in benzene at 60 °C gave the fluorenones **7b** or **7c** after acidic workup (54% and 58%, respectively). Consequently the remote metalation at C2′ and cyclization is faster than the lateral metalation of the chain of the substrate. Notably, reaction C gave **7b** in lower yield (10%). Because of the drastic reaction conditions used, the corresponding reactions of **6d–g** failed. For the preparation of 1-substituted fluorenones, the sequence A + B is thus to be preferred.

We next embarked on an investigation of the deprotonation of biphenyl-3- and -4-carboxylic acids (**4** and **5**) by varying the base, the solvent, the metalation temperature, and the exposure times (Scheme 2). Whereas acid **4** in principle offers selection of either of the two possible *ortho* substitutions (C2 and C4), **5** can be metalated only in the C3 position for symmetry reasons. Biphenyl-3- and -4-carbox-

ylic acid moieties are present in numerous biologically active molecules.[24,25] The acids **4** and **5** were prepared by Suzuki coupling between phenylboronic acid and 3- or 4-bromobenzoic acids in the presence of Pd/C (10%) and triphenylphosphane (0.2 equiv.) (65% and 85% yield, respectively).[26]



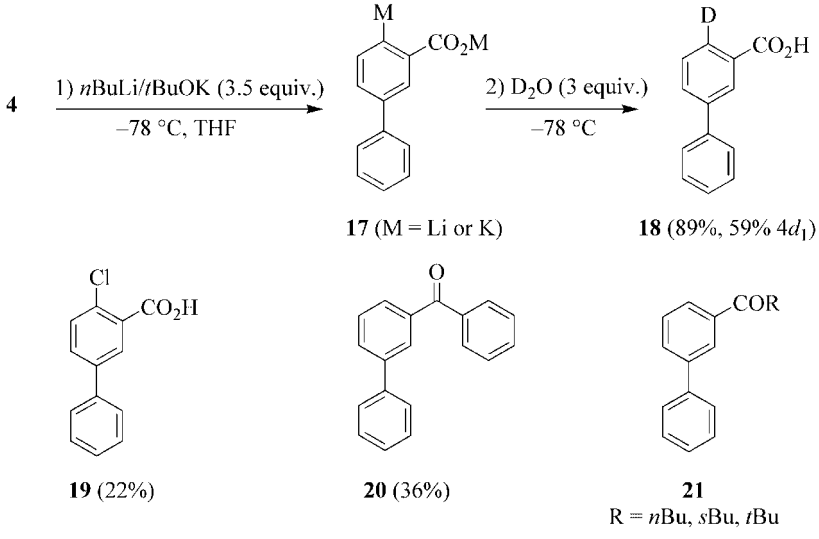
Scheme 2.

Metalation of **4** was achieved with LICKOR (3.5 equiv.) in THF for 2 h at –78 °C (Scheme 3). Trapping of the dianion **17** with D_2O at –78 °C [external quench (EQ) conditions] gave **18** in which 59% of the deuterium was incorporated at the C4 carbon (89%) (determined by ^1H NMR and FIMS). The percentage of deuterium was defined as absolute regioselectivity of the metalation. It was assigned as decreased intensity of the signal in relation to the averaged intensities of the unaffected positions: 2, 5, and 6 (1.00 ± 0.05 unit/1 H). The two-dimensional COSY ^1H-^1H spectra of **4** and **18** confirmed the correct deuterium regiochemistry of the reaction products. Quenching with hexachloroethane afforded 4-chlorobiphenyl-3-carboxylic acid (**19**), which was isolated in 22% yield after column chromatography and recrystallization.

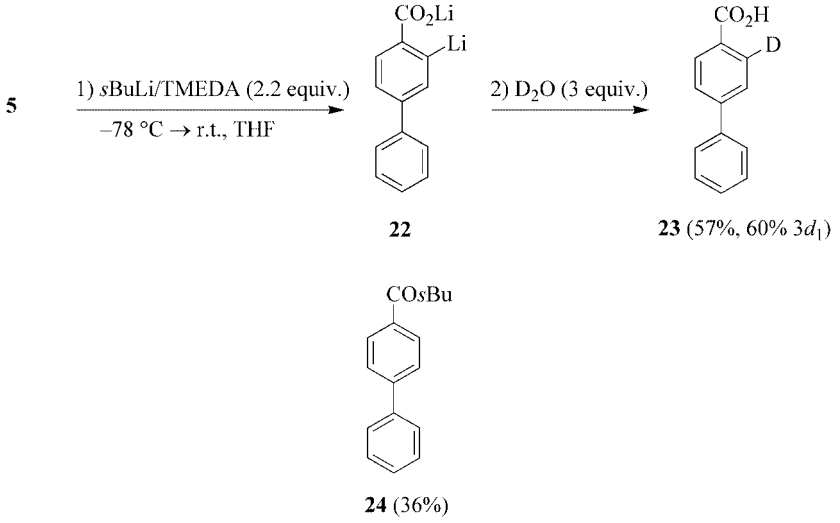
The acid **4**, LTMP, and Me_3SiCl did not react under in situ quench conditions.[27] With LICKOR (3.5 equiv.) in benzene at 20 °C, (biphenyl-3-yl)(phenyl)methanone (**20**) was the only product formed (36%). It has been reported in the literature that benzene is metalated by the superbasic *n*-butyllithium/*t*BuOK mixture, affording phenyl potassium (C_6H_5K), the purity of which was reported to be highly dependent on reaction conditions.[28] Since alkyl and arylpotassium are weakly nucleophilic,[29,30] PhLi must be the reactive nucleophilic species that reacts with the lithium salt of **4** to give **20**.

Alkyllithium bases (*n*BuLi, *s*BuLi, and *t*BuLi) and LTMP are not suitable to metalate **4**. Nucleophilic addition of RLi to the carboxylate again provided the 1,2-addition products **21**.[31] Furthermore, addition of HMPA, TMEDA, or PMDTA at –78 °C was virtually without effect.

Biphenyl-4-carboxylic acid (**5**) was also subjected to a series of bases (Scheme 4). Alkyllithiums are again too nucleophilic, whereas LICKOR and LTMP do not react. It was found that the 1:1 *s*BuLi/TMEDA complex (2.2 equiv.) was able to metalate the acid **5** regioselectively, affording the dilithio dianion **22**. Subsequent deuterolysis with D_2O gave **23** (57%) with 60% deuterium incorporation (evaluated by NMR). The $3d_0/3d_1$ isotope ratio was determined to be 39.4:60.4 by FIMS of chromatographed material. Complexation of the carboxylate by the alkyllithium base is presumably once again the predominant factor that governs the reaction rate. The 1,2-addition is competitive, since 1-(biphenyl-4-yl)-2-methylbutan-1-one (**24**) was also isolated in 36% yield.



Scheme 3.



Scheme 4.

Experimental Section

General: For standard working practices, see ref.[32,33]. Metalation reactions were carried out under argon in oven-dried glassware. Tetrahydrofuran was dried from sodium benzophenone ketyl. Benzene was distilled from calcium hydride. NMR spectra were recorded on 200 or 400 MHz spectrometers. ^{13}C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, chemical shifts are recorded relative to the internal TMS (tetramethylsilane) reference signal. For [D_6]DMSO and [D_6]acetone used as solvents, chemical shifts are given relative to the solvent signals.

3-Substituted Biphenyl-2-carboxylic Acids 6a–k from Biphenyl-2-carboxylic Acid (3). General Procedure (Reaction A): *s*BuLi (1.3 M in cyclohexane, 44 mL, 57.2 mmol) was added dropwise under argon at –78 °C − over a period of ca. 30 min − to a vigorously stirred solution of biphenyl-2-carboxylic acid (**3**, 5 g, 25.22 mmol) in anhydrous THF (180 mL). A deep red-orange coloration appeared during addition of the organolithium. After 2.5 h stirring at –78 °C, the mixture was treated with an excess of the appropriate electrophile. The solution was then allowed to warm overnight to ambient temperature, and water (30 mL) was added. The aqueous phase was washed twice with diethyl ether (40 mL) and shaken, and was then acidified with HCl (4 M, pH 1). The aqueous phase was extracted with diethyl ether (4 × 20 mL). The combined ether phases were washed with water (2 × 25 mL) and dried with $MgSO_4$. Filtration and concentration in vacuo gave the crude acids **6a**–**k**, which were purified by recrystallization for characterization in each case.

3-Deuteriobiphenyl-2-carboxylic Acid (6a): This compound was prepared as described in the General Procedure, with quenching with D_2O (3.8 mL, 210 mmol) to give **6a** as a white solid (4.98 g, 99%). The isotope ratio determined by ^1H NMR (doublet at δ = 7.94 ppm attributed to H3) and FIMS was found to be $3d_0$:$3d_1$ 30:70. ^1H NMR (200 MHz, $CDCl_3$): δ = 10.63 (s, 1 H, COOH), 7.94 (d, J = 7.3 Hz, 0.3 H), 7.56–7.55 (m, 1 H), 7.46–7.26 (m, 7 H).

3-Methylbiphenyl-2-carboxylic Acid (6b): This compound was prepared as described in the General Procedure, with quenching with iodomethane (4.7 mL, 75.6 mmol) to give **6b** as a white solid [recrystallization heptane/ethyl acetate, m.p. 133.4–134.4 °C, ref.[34,35] 132–133 °C, 4.29 g, 80%]. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.50 (s, 1 H), 7.39–7.32 (m, 6 H), 7.20 (m, 1 H), 7.19 (d, J = 2.4 Hz, 1 H), 2.43 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.2, 140.6, 140.2, 135.4, 132.1, 129.7, 129.2 (2 C), 128.3 (3 C), 127.5, 127.5, 19.9 ppm. IR (KBr): $\tilde{\nu}$ = 2951–2643 (br), 1699, 1458, 1284 cm^{-1}. $C_{14}H_{12}O_2$ (212.24): calcd: C 79.23, H 5.70; found C 79.44, H 5.72.

3-Ethylbiphenyl-2-carboxylic Acid (6c): This compound was prepared as described in the General Procedure, with quenching with iodoethane (6 mL, 75.6 mmol) to give **6c** as a white solid [recrystallization heptane/ethyl acetate, m.p. 140–141 °C, 3.60 g, 63%]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.35 (m, 6 H), 7.26–7.20 (m, 2 H), 2.76 (dd, J = 7.9 Hz and J = 7.4 Hz, 2 H), 1.28 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.1, 141.5, 140.6, 140.0, 131.7, 129.8, 128.4 (2 C), 128.3 (2 C), 127.6, 127.5, 127.5, 26.8, 15.7 ppm. IR (KBr): $\tilde{\nu}$ = 2969, 1689, 1588, 1463, 1286, 1253 cm^{-1}. $C_{15}H_{14}O_2$ (226.27): calcd: C 79.62, H 6.24; found C 79.57, H 6.21.

3-Chlorobiphenyl-2-carboxylic Acid (6d): This compound was prepared as described in the General Procedure, with quenching with hexachloroethane (17.9 g, 75.6 mmol) to give **6d** as a white solid [recrystallization heptane/ethyl acetate, m.p. 184–185 °C, ref.[36] 184–186 °C, 4.23 g, 72%]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 6 H), 7.32–7.28 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 168.9, 142.9, 141.3, 135.9, 132.2, 132.0, 130.3, 130.3 (2 C), 130.0 (2 C), 129.8 ppm. IR (KBr): $\tilde{\nu}$ = 3025–2786 (br), 1699, 1560, 1455, 1294 cm^{-1}.

3-Bromobiphenyl-2-carboxylic Acid (6e): This compound was prepared as described in the General Procedure, with quenching with $C_2Br_2Cl_4$ (24.6 g, 75.6 mmol) to give **6e** as a white solid [recrystallization heptane/ethyl acetate, m.p. 185–186 °C, 4.97 g, 71%]. ^1H NMR (400 MHz, [D_6]acetone): δ = 11.30 (s, 1 H), 7.71–7.59 (m, 1 H), 7.45–7.30 (m, 7 H) ppm. ^{13}C NMR (50 MHz, [D_6]acetone): δ = 169.5, 143.0, 141.2, 131.5, 130.7, 128.8, 128.5 (2 C), 128.3 (3 C), 128.2, 119.3 ppm. IR (KBr): $\tilde{\nu}$ = 3029–2801 (br), 1699, 1552, 1456 cm^{-1}.

3-Iodobiphenyl-2-carboxylic Acid (6f): This compound was prepared as described in the General Procedure, with quenching with iodine (19.19 g, 75.2 mmol) to give **6f** as a white solid [recrystalli-

zation heptane/ethyl acetate, m.p. 169–170 °C, 5.97 g, 73%]. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 11.91 (s, 1 H), 7.94 (dd, J = 7.9 Hz and J = 1.0 Hz, 1 H), 7.47–7.38 (m, 6 H), 7.28–7.25 (m, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 170.9, 142.7, 142.3, 141.7, 139.9, 132.4, 131.5, 130.3, 130.2 (2 C), 129.8 (2 C), 93.7 ppm. IR (KBr): $\tilde{\nu}$ = 2903, 1688, 1552, 1287 cm^{-1}. $C_{13}H_9IO_2$ (324.11): calcd: C 48.17, H 2.80; found C 48.25, H 2.80.

3-(Methylthio)biphenyl-2-carboxylic Acid (6g): This compound was prepared as described in the General Procedure, with quenching with dimethyl disulfide (6.8 mL, 77 mmol) to give **6g** as a white solid [recrystallization heptane/ethyl acetate, m.p. 115–116 °C, 5.0 g, 81%]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.26 (s, 1 H, COOH), 7.45–7.35 (m, 7 H), 7.21 (dd, J = 7.2 Hz and J = 0.8 Hz, 1 H), 2.51 (s, 3 H, SCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.2, 140.8, 139.9, 136.6, 132.6, 130.2, 128.4 (2 C), 128.3 (2 C), 127.7, 127.4, 126.8, 17.6 ppm. IR (KBr): $\tilde{\nu}$ = 3035–2905 (br), 1685, 1596, 1450, 1404, 1132 cm^{-1}. $C_{14}H_{12}O_2S$ (244.31): calcd: C 68.83, H 4.95; found C 69.03, H 4.85.

3-(Trimethylsilyl)biphenyl-2-carboxylic Acid (6h): This compound was prepared as described in the General Procedure, with quenching with chlorotrimethylsilane (8.20 g, 75.2 mmol) to give **6h** as a white solid [recrystallization heptane/ethyl acetate, m.p. 143–144 °C, 6.69 g, 98%]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.4 Hz, 1 H), 7.46 (dd, J = 7.9 Hz and J = 7.3 Hz, 1 H), 7.37–7.34 (m, 6 H), 0.32 (s, 9 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 177.7, 140.9, 140.1, 138.7, 137.1, 133.5, 130.7, 129.3, 128.3 (4 C), 127.3, 0.0 (3 C). $C_{16}H_{18}O_2Si$ (270.4): calcd: C 71.07, H 6.71; found C 71.11, H 6.81.

Tributylstannyl 3-(Tributylstannyl)biphenyl-2-carboxylate (6i′): Treatment of biphenyl-2-carboxylic (**3**, 1.0 g, 5.06 mmol) and *s*BuLi (1.3 M in cyclohexane, 8.6 mL, 11.1 mmol) in THF (30 mL) was followed by quenching with excess tri-*n*-butyltin chloride (4 mL, 15.16 mmol). After the system had been allowed to warm to room temperature and the solvents had been removed in vacuo, heptane (15 mL) was added to the residue. The insoluble component was filtered off and the filtrate was concentrated with a rotavap. Volatiles were removed under vacuum (4 mbar) at 200 °C and the resulting orange residue was chromatographed on neutral alumina (cyclohexane/ethyl acetate 8:2) to give **6i′** as a colorless oil (13.33 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57 (dd, J = 7.4 Hz and J = 20.2 Hz, 1 H), 7.39 (m, 1 H), 7.32–7.19 (m, 5 H), 7.24 (dd, J = 7.4 Hz and J = 7.9 Hz, 1 H), 1.38–1.61 (m, 12 H), 1.21–1.37 (m, 12 H), 1.00–1.16 (m, 12 H), 0.88 (t, 18 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.6, 147.2, 144.5, 143.2, 137.8, 135.5, 130.8, 129.2, 128.4, 127.5, 126.2, 29.3, 27.7, 27.5, 27.1, 16.3, 13.8, 13.6, 11.5 ppm.

3-Hydroxy-7-phenylisobenzofuran-1(3*H*)-one (14): This compound was prepared as described in the General Procedure, with quenching with freshly distilled DMF (5.87 mL, 75.6 mmol) to give **14** (via **6j**) as a white solid [recrystallization heptane/ethyl acetate, m.p. 145–147 °C, 4.57 g, 80%]. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.75 (dd, J = 7.9, J = 7.3 Hz, 1 H), 7.61 (d, J = 7.3 Hz, 1 H), 7.53–7.49 (m, 3 H), 7.46–7.40 (m, 3 H), 6.60 (s, 1 H), 6.53 (s, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 167.6, 148.1, 142.0, 136.2, 134.1, 132.1, 129.3, 128.2 (2 C), 127.8, 122.8 (2 C), 122.1, 96.1 ppm. IR (KBr): $\tilde{\nu}$ = 2883, 1693, 1551, 1442, 1286, 1145 cm^{-1}. $C_{14}H_{10}O_3$ (226.23): calcd: C 74.33, H 4.46; found C 74.53, H 4.56.

3,7-Diphenylisobenzofuran-1(3*H*)-one (15): This compound was prepared as described in the General Procedure, with quenching with freshly distilled benzaldehyde (7.72 mL, 75.6 mmol) to give **15** (via **6k**) as a white solid [recrystallization diethyl ether/heptane, m.p. 91–92 °C, 6.72 g, 93%]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.57 (m, 3 H), 7.52–7.45 (m, 4 H), 7.42–7.25 (m, 6 H), 6.37 (s, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 169.2, 151.0, 142.6, 136.6, 136.2, 134.0, 131.0, 129.5, 129.1 (2 C), 128.9, 128.3 (3 C), 127.9, 126.9 (2 C), 121.6 (2 C), 121.4 ppm. IR (KBr): $\tilde{\nu}$ = 3057, 1765, 1013 cm^{-1}. $C_{20}H_{14}O_2$ (286.32): calcd: C 83.90, H 4.93; found C 83.84, H 4.95.

***meta*-Terphenyl-2′-carboxylic Acid (13):** Triphenylphosphane (95 mg, 0.34 mmol), bistriphenylphosphane dichloropalladium (127 mg, 0.17 mmol), and iodobenzene (0.75 mL, 6.88 mmol) were successively added, under argon, to a solution of **6i′** (2.69 g, 3.44 mmol) in xylene (25 mL). After having been heated at reflux for 24 h, the mixture was allowed to cool to room temp., filtered, and extracted with aq. NaOH (2 M). The aqueous layer was washed twice with diethyl ether (40 mL), acidified with aq. HCl (4 M, 4 mL), and extracted with diethyl ether (2 × 60 mL). The combined ether layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was recrystallized (heptane/ethyl acetate). The product **13** was isolated as a white solid (m.p. 188–189 °C, ref.[37] 191–193 °C, 0.56 g, 59%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.56–7.25 (m, 13 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.5, 140.3 (2 C), 131.7, 129.6, 128.9 (2 C), 128.4 (4 C), 128.3 (4 C), 128.1, 127.6 (2 C) ppm.

1-Substituted 9*H*-Fluoren-9-ones 7b–g by Intramolecular Friedel–Crafts Acylation of Acids 6b–g (Reaction B). General Procedure: The appropriate compound (**6b**–**g**, 9.4 mmol) was dissolved in methanesulfonic acid (≈ 50 equiv.) in a round-bottomed flask with a magnetic stirrer, and the reaction mixture was warmed to 60 °C. A dark red color appeared rapidly. The reaction was followed by TLC until total conversion of the starting acid was observed. The mixture was then poured into water (25 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic layer was washed successively with water (2 × 15 mL), satd. $NaHCO_3$ (15 mL), and water (15 mL), and was then dried with $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was recrystallized (heptane/ethyl acetate).

1-Methyl-9*H*-fluoren-9-one (7b): This compound was prepared from **6b** as described in the General Procedure given above. Yellow solid (m.p. 98–99 °C, ref.[38] 97–98 °C, 1.73 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 7.4 Hz, 1 H), 7.43 (ddd, J = 7.4, J = 6.9, J = 7.9 Hz, 2 H), 7.34–7.29 (m, 2 H), 7.24 (m, 1 H), 7.03 (m, 1 H), 2.60 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 195.0, 144.7, 143.8, 139.4, 134.3, 133.9, 131.8, 130.8, 128.8, 123.7, 119.9 (2 C), 117.8, 17.7 ppm.

1-Methyl-9*H*-fluoren-9-one (**7b**) was also prepared from **6b** by metalation with LICKOR (reaction D), **6b** (0.54 g, 2.52 mmol) in dry THF (20 mL) being added dropwise to a solution of LICKOR (5.54 mmol, preparation: see reaction C, General Procedure) in dry benzene (10 mL) at 60 °C. The mixture was stirred for 4–5 h at 60 °C, after which water (20 mL) was added. The reaction mixture was extracted with ethyl acetate, the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo, and the residue was chromatographed (cyclohexane/ ethyl acetate) to give **7b** (0.27 g, 54%).

1-Ethyl-9*H*-fluoren-9-one (7c): This compound was prepared from **6c** as described in the General Procedure given above. Yellow solid (m.p., 93.6–94.4 °C, ref.[39] 91–93 °C, 1.72 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.4 Hz, 1 H), 7.48–7.43 (m, 2 H), 7.36–7.32 (m, 2 H), 7.26 (dd, J = 1.5 Hz and J = 7.4 Hz, 1 H), 7.08 (dd, J = 1.5 Hz and J = 6.9 Hz, 1 H), 3.07 (q, J = 7.5 Hz, 2 H), 1.25 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.8, 146.0, 144.9, 143.8, 134.2 (2 C), 130.1 (2 C), 128.8, 123.8 (2 C), 119.9, 117.9, 24.5, 14.7 ppm.

Compound **7c** was also prepared from **6c** (2.52 mmol) by metalation with LICKOR (reaction D) (304 mg, 58%). See second preparation of **6b**.

1-Chloro-9*H*-fluoren-9-one (7d): This compound was prepared from **6d** as described in the General Procedure given above. Yellow solid (m.p., 138–139 °C, ref.[40] 137–137.8 °C, 1.65 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 7.4 Hz, 1 H), 7.47 (d, J = 3.9 Hz, 2 H), 7.39–7.36 (m, 2 H), 7.30 (m, 1 H), 7.17 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.7, 146.4, 142.4, 135.1, 134.6, 133.7, 132.6, 130.8, 129.6, 129.3, 124.3, 120.3, 118.6 ppm.

1-Bromo-9*H*-fluoren-9-one (7e): This compound was prepared from **6e** as described in the General Procedure given above. Yellow solid (m.p. 132.5–133.5 °C, ref.[40] 134–134.3 °C, 2.34 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 7.4 Hz, 1 H), 7.46 (m, 2 H), 7.43 (d, J = 7.4 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 1 H), 7.26–2.30 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.9, 146.8, 142.2, 135.2, 134.7, 134.1, 133.6, 131.0, 129.5, 124.3, 120.4, 119.1, 118.6 ppm.

1-Iodo-9*H*-fluoren-9-one (7f): This compound was prepared from **6f** as described in the General Procedure given above. Yellow solid (m.p. 147–148.5 °C, ref.[40] 144–145 °C, 2.65 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 2 H), 7.50–7.47 (m, 3 H), 7.28 (m, 1 H), 7.31 (m, 1 H), 7.12 (dd, J = 7.9 Hz and J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 191.6, 147.0, 141.7, 140.4, 134.9, 134.9, 134.9, 129.5, 124.5, 120.0 (2 C), 119.9, 91.5 ppm.

1-(Methylthio)-9*H*-fluoren-9-one (7g): This compound was prepared from **6g** as described in the General Procedure given above. Yellow solid (m.p. 167–168 °C, 1.94 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 7.4 Hz, 1 H), 7.48–7.43 (m, 2 H), 7.37 (dd, J = 7.4 Hz and J = 7.9 Hz, 1 H), 7.27 (m, 1 H), 7.22 (d, J = 7.4 Hz, 1 H), 7.05 (d, J = 7.9 Hz, 1 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.1, 145.4, 143.1, 141.4, 134.4, 134.1, 129.1, 128.8, 123.8 (2 C), 120.2, 115.7, 13.6 ppm.

1-Phenyl-9*H*-fluoren-9-one (16): This compound was prepared from **13** as described in the General Procedure given above. Yellow solid (m.p. 119–120 °C, ref.[17] 119–120 °C, 0.99 g, 41%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.37 (m, 10 H), 7.30–7.13 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.0, 145.3, 143.4, 142.1, 137.3, 134.6, 134.4, 134.1, 131.4, 129.0 (2 C), 128.7, 127.7 (2 C), 124.2, 123.9, 120.2, 119.9, 119.1 ppm.

1-Substituted 9*H*-Fluoren-9-ones 7a, 7b, 7d–g from Biphenyl-2-carboxylic Acid (3) (Reaction C). General Procedure: *n*-Butyllithium (4.5 mL, 7.8 mmol) was added at ambient temperature to a suspension of potassium *tert*-butoxide (792 mg, 7.0 mmol) in benzene (10 mL). After the mixture had been stirred for 5 min, the LICKOR base was transferred into a round flask containing biphenyl-2-carboxylic acid (**3**, 400 mg, 2.02 mmol) in benzene (5 mL). Stirring at 60 °C was maintained for an hour. The system was allowed to cool to room temp., *n*BuLi (2.5 mL, 4.05 mmol) was added dropwise, and the mixture was stirred at 60 °C for an additional 2 hours. After gradually cooling to room temp., the solution was quenched with the electrophile (40.4 mmol) in benzene (6 mL). The yellow mixture was stirred overnight, after which water (30 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 30 mL), acidified with aq. HCl (2 M), and extracted with ethyl acetate (3 × 30 mL). After concentration in vacuo, the crude 1-substituted 9*H*-fluoren-9-ones **7a**, **7b**, **7d**–**g** were purified by chromatography on silica gel (cyclohexane/ethyl acetate, 90:10).

1-Deuterio-9*H*-fluoren-9-one (7a): Quenching with D_2O (40.4 mmol) gave **7a** as a yellow solid (m.p. 80–82 °C, 256 mg, 70%). The isotope ratio was determined by ^{1}H NMR and FIMS: $1d_0$:$1d_1$ 0:100. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63 (d, 1 H, J = 7.4 Hz), 7.46 (m, 4 H), 7.27 (m, 2 H) ppm.

1-Methyl-9*H*-fluoren-9-one (7b): Quenching with iodomethane gave **7b** as a yellow solid (39 mg, 10%). See above for spectroscopic and analytical characterization.

1-Chloro-9*H*-fluoren-9-one (7d): Quenching with hexachloroethane gave **7d** (130 mg, 30%). See above for spectroscopic and analytical characterization.

1-Bromo-9*H*-fluoren-9-one (7e): Quenching with $C_2Br_2Cl_4$ gave **7e** (251 mg, 48%). See above for spectroscopic and analytical characterization.

1-Iodo-9*H*-fluoren-9-one (7f): Quenching with elemental iodine gave **7f** (266 mg, 43%). See above for spectroscopic and analytical characterization.

1-Methylthio-9*H*-fluoren-9-one (7g): Quenching with dimethyl disulfide gave **7g** (224 mg, 49%). See above for spectroscopic and analytical characterization.

Biphenyl-3-carboxylic Acid (4) and Biphenyl-4-carboxylic Acid (5): 3-Bromobenzoic acid or 4-bromobenzoic acid (3.5 g, 17.4 mmol), phenylboronic acid (2.7 g, 20.9 mmol), Pd/C (907 mg, 0.86 mmol, 10% weight, 3230H type), triphenylphosphane (808 mg, 3.08 mmol) and dimethoxyethane (60 mL) were stirred under argon for 20 min at room temperature. Aqueous Na_2CO_3 (2 M, 33 mL) was added and the mixture was stirred at 85 °C for 24 h. After the mixture had cooled to room temp., diethyl ether was added. After filtration through celite, the filtrate was washed with water (3 × 100 mL), and the aqueous layer was acidified with aq. HCl (4 M) until the pH reached 1. The aqueous layer was washed with diethyl ether (6 × 50 mL), the combined ether layer was dried with $MgSO_4$ and concentrated in vacuo, and the residue was recrystallized (heptane/ethyl acetate) to give the product.

Biphenyl-3-carboxylic acid (**4**) was obtained as white crystals (m.p. 112–114 °C, ref.[41] 112–114 °C, 2.24 g, 65%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.68 (s, 1 H), 8.37 (s, 1 H), 8.11 (d, J = 7.8 Hz, 1 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.54–7.51 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.2, 141.6, 140.0, 132.4, 129.8, 128.9 (2 C), 128.9 (2 C), 128.8, 127.8, 127.1 (2 C) ppm.

Biphenyl-4-carboxylic acid (**5**) was recrystallized from chloroform (m.p. 224–225 °C, ref.[41] 227–229 °C, 2.93 g, 85%). ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 8.05 (d, J = 8.2 Hz, 2 H), 7.75–7.73 (m, 4 H), 7.47–7.45 (m, 3 H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 167.1, 144.3, 139.0, 129.9 (2 C), 129.6, 129.0 (2 C), 128.2, 126.9 (2 C), 126.8 (2 C) ppm.

4-Deuteriobiphenyl-3-carboxylic Acid (18): *n*-Butyllithium (3.52 mL, 6.1 mmol) was added at –78 °C to a suspension of potassium *tert*-butoxide (627 mg, 5.54 mmol) in dry THF (10 mL). After the mixture had been stirred for 5 min, biphenyl-3-carboxylic acid (**4**, 500 mg 2.52 mmol) in dry THF (20 mL) was added dropwise at –78 °C to the LICKOR superbase. Vigorous stirring was maintained for 2 h, and D_2O (150 μL, 8.3 mmol) in dry THF (4 mL) was added at –78 °C. The mixture was stirred overnight at room temp. and water (20 mL) was added. The aqueous layer was washed with diethyl ether (2 × 20 mL) and acidified (pH 1) with aq. HCl (2 M). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined ether layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was recrystallized (heptane/ethyl acetate) to give **18** as a white solid. The isotope ratio determined by ^{1}H NMR (multiplet at δ = 8.11 ppm attributed to H4) was found to be $4d_0$:$4d_1$ 41:59. ^{1}H NMR (400 MHz, $CDCl_3$): δ =

8.37 (m, 1 H), 8.11 (m, 0.41 H, residual H4), 7.86 (m, 1 H), 7.69–7.38 (m, 6 H) ppm.

4-Chlorobiphenyl-3-carboxylic Acid (19): Biphenyl-3-carboxylic acid (**3**, 375 mg 1.9 mmol) in dry THF (5 mL) was added dropwise at –78 °C to a solution of LICKOR (5.7 mmol, see preparation above) in dry THF (7 mL). After the mixture had been vigorously stirred at –30 °C for 1.5 h, hexachloroethane (2.689 g, 11.4 mmol) in dry THF (5 mL) was added. Similar workup followed by chromatography (cyclohexane/ethyl acetate 9:1) and recrystallization (heptane/ethyl acetate) gave 4-chlorobiphenyl-3-carboxylic acid (**19**) as a white solid (m.p. 192 °C, 97 mg, 22%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.16 (d, J = 2.5 Hz, 1 H), 7.84 (dd, J = 2, J = 8.4 Hz, 1 H), 7.71–7.73 (m, 2 H), 7.63 (d, J = 8.4 Hz, 1 H), 7.52–7.50 (m, 2 H), 7.44 (d, J = 6.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 166.6, 139.0, 138.0, 131.9, 131.5, 130.8, 129.0, 128.7, 128.1, 126.7, 126.6 ppm. HRMS calcd for $C_{13}H_9{}^{35}ClO_2$: calcd: 232.0291; found 232.0292.

(Biphenyl-3-yl)(phenyl)methanone (20):[42] *n*-Butyllithium (3.52 mL, 6.1 mmol) was added at 20 °C to a suspension of potassium *tert*-butoxide (627 mg, 5.54 mmol) in dry benzene (10 mL). After the mixture had been stirred for 5 min, biphenyl-3-carboxylic acid (**4**, 500 mg 2.52 mmol) in dry THF (20 mL) was added dropwise to the LICKOR superbase. Vigorous stirring was maintained for 2 h and water was added. Conventional workup gave **20** as a white solid (m.p. 94 °C) after chromatography on silica gel (234 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.22–8.08 (m, 3 H), 7.97–7.89 (m, 3 H), 7.88–7.77 (m, 4 H), 7.74–7.68 (m, 1 H), 7.68–7.56 (m, 2 H).

3-Deuteriobiphenyl-4-carboxylic Acid (23): Biphenyl-4-carboxylic acid (**5**, 500 mg, 2.52 mmol) dissolved in dry THF (10 mL), was added dropwise under argon at –78 °C − over a period of 30 min − to a vigorously stirred solution of a 1:1 *s*BuLi/TMEDA complex (5.54 mmol) in anhydrous THF (10 mL). After 2 hours stirring at –78 °C, the mixture was treated with an excess of D_2O (150 μL, 8.3 mmol). The resulting solution was allowed to warm to ambient temperature and water (20 mL) was added. The aqueous layer was washed with diethyl ether (2 × 20 mL), shaken, and then acidified with HCl (2 M, pH 1). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with $MgSO_4$. Filtration and concentration in vacuo gave the crude carboxylic acid **23**, which was purified by chromatography (cyclohexane/ethyl acetate 9:1) (286 mg, 57%). The isotope ratio determined by ^{1}H NMR (multiplet at δ = 8.05 ppm attributed to H_3-$H_{3'}$) was found to be $3d_0$:$3d_1$ 40:60. The $3d_0$/$3d_1$ isotope ratio was determined to be 39.4:60.4 by FIMS of chromatographed material. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (m, 1.4 H, residual H3–H3′), 7.97–7.71 (m, 4 H), 7.59–7.39 (m, 3 H) ppm.

1-(Biphenyl-4-yl)-2-methylbutan-1-one (24):[43] White solid (216 mg, 36%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.10–8.01 (m, 2 H), 7.87–7.69 (m, 4 H), 7.56–7.36 (m, 3 H), 3.56 (m, 1 H), 1.71 (m, 1 H), 1.12–1.10 (m, 3 H), 1.42 (m, 1 H), 0.85 (t, 3 H) ppm.

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