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Full Paper

Uncatalyzed CO_2Li-Mediated S_NAr Reaction of *Unprotected* Benzoic Acids via Silicon Trickery

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The alkyl and aryllithium nucleophilic aromatic substitution (S_NAr) displacement of a fluoro or methoxy group from *unprotected* 2-fluoro/methoxybenzoic acids is discussed. It was discovered that a TMS group located at the C6-position *ortho* to the carboxyl group shields effectively the carboxylate against nucleophilic attack, thus reducing dramatically ketone formation, and reorients nucleophilic substitution to the C2-position. The reactions with fluoro-substituted substrate **7** proceed efficiently; in contrast, the use of methoxy-functionalized benzoic acid **8** only affords moderate yields with *s*-BuLi and PhLi. This uncatalyzed coupling reaction, which provides a direct access to biaryl compounds, presumably proceeds by an addition–elimination sequence via intermediate formation of a resonance-stabilized pentavalent silalactone-Meisenheimer complex.

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Introduction

The *unprotected* carboxyl-directing metalation group exhibits a remarkable degree of regiocontrol between non-equivalent *ortho* centres in directed *ortho* metalation chemistry (DoM, Fig. 1).[1] As deprotonation of 2-anisic acid (**2**) occurs exclusively at the C6-position adjacent to the carboxylate with the 1 : 1 complex *s*-BuLi/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at −78°C, a complete reversal of regioselectivity is observed with the Schlosser–Lochmann superbase (*n*-BuLi/*t*-BuOK).[2] Exposing 2-fluorobenzoic acid (**1**) to lithium 2,2,6,6-tetramethylpiperidide (LTMP) at −78°C deprotonates the C3-position *ortho* to the fluorine, whereas 2-chloro- and 2-bromobenzoic acids ((**3**) and (**4**)) are exclusively metalated in the vicinity of the carboxylate.[3]

In the absence of aprotic Lewis base additive, the reaction follows a different pathway. In the benzene series, direct nucleophilic aromatic substitution (S_NAr) coupling of **1** and **2** is observed with common organolithium reagents (*n*-BuLi, *s*-BuLi, *t*-BuLi, and PhLi) leading to 2-alkyl and arylbenzoic acids. However, the process is hampered by the simultaneous susceptibility of the polar species to react with the lithium carboxylate (nucleophilic addition (NA)), providing ketone by-products. In the naphthalene series, substitution of the *ortho*-fluoro and methoxy groups of **5** and **6** by alkyl, vinyl, or aryllithiums, lithioamides, or Grignard reagents occurs exclusively, furnishing the corresponding substitution products in good-to-excellent yields.[4]

We are now able to propose a more rigorous and convenient approach to circumvent the issue encountered with **1** and **2**. This new approach is based on the introduction of a trialkylsilyl group at the C6-position to shield the carboxylate in the adjacent position, thus reorienting the nucleophilic attack at the C2-position. The developed strategy relies on the following observations: (1) based on sparse information, the steric congestion resulting from the silyl group is able to reduce the electrophilicity of a carboxylate;[5] (2) arylsilanes are stable to alkyllithium reagents;[6] (3) arylsilanes bearing an electron-withdrawing function tolerate *ipso*-desilylation processes;[7] and (4) introduction of a silyl group at C6 should provide useful precursors for cross-coupling reactions.[8]

Results and Discussion

The original principle of regiocontrol established by the ‘silyl trick’[9] reported herein is illustrated by the transformations of 2-fluoro- and 2-methoxy-6-(trimethylsilyl)benzoic acids ((**7**) and (**8**)). Compound **8** was prepared by metalation of 2-methoxybenzoic acid (**2**) followed by chlorotrimethylsilane (TMSCl) trapping using the in situ quench (ISQ) technique[10] (89 %, Scheme 1). Because 2-fluorobenzoic acid (**1**) cannot be metalated at the position C6 adjacent to the carboxylate (see Fig. 1), an access to 2-fluoro-6-(trimethylsilyl)benzoic acid (**7**) was envisioned through the acid **10**, which was easily prepared by lithiation and carboxylation of 1-bromo-3-fluorobenzene (**9**). The halogen-lithium exchange/TMSCl-quench sequence (**10** → **7**) was studied under several conditions (Table 1). Under external quench (EQ) conditions at −78°C, besides the expected product **7**, 2-fluorobenzoic acid (**1**) was obtained in 28 % yield (entry 1). At −90°C, an 82 % yield of the expected product **7** was attained, and the amount of **1** produced decreased to 10 % (entry 2).

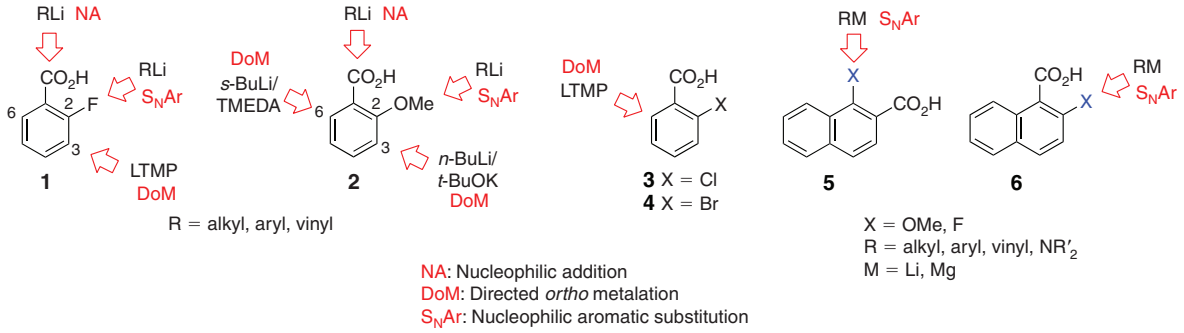
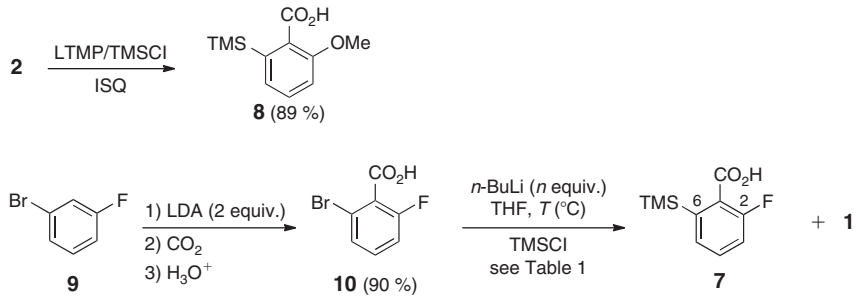


Fig. 1. Reactivity of unprotected benzoic acids towards strong bases.



Scheme 1. Preparation of 2-fluoro- and 2-methoxy-6-(trimethylsilyl)benzoic acids (**7**) and (**8**).

Table 1. Br-Li exchange/(TMSCl or D_2O) quench sequence (10 → 7 or 1-6d_1)

Entry	T [°C]	Add[A]	n[B]	EX[C]	7, 1-6d_1[D]	1	10[E]
1	−78	EQ	2	TMSCl	65 (**7**)	28	0
2	−90	EQ	2	TMSCl	82 (47*) (**7**)	10	0
3	−90 → rt	ISQ	2.5	TMSCl	70 (54*) (**7**)	0	0
4	−90 → rt	ISQ	2.5	D_2O	30 (**1**-6d_1)	0	65
5	−90 → rt	ISQ	6	D_2O	52 (**1**-6d_1)	0	48

[A]Addition mode – EQ: external quench (*n*-BuLi was allowed to react with **10** at T (°C) before addition of the electrophile); ISQ: internal quench (**10** and the electrophile were pre-mixed before addition of *n*-BuLi).
[B]*n*-BuLi (*n* equiv.).
[C]The amount of electrophile (EX) used was 4 equiv., except for entry 5 (8 equiv.).
[D]Crude yields (%), estimated by ^{1}H NMR. Isolated yields (recrystallized or chromatographed) are denoted by an asterisk (*).
[E]Amount (%) of unreacted starting acid **10**.

These results are reproducible; however, **1** and **7** proved difficult to separate by recrystallization or chromatographic means.

Two reasons can be postulated to explain the formation of **1**: (1) the organometallic intermediate reacts with water traces contained in the solvent and (2) the intermediate abstracts hydrogen from the solvent.

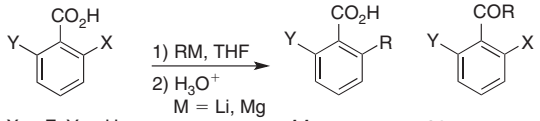
Formation of **1** was shown not to arise from the presence of water traces by changing the order of reagent addition. *n*-BuLi was added to sodium-dried THF (this would remove any moisture traces), and neat 2-bromo-6-fluorobenzoic acid (**10**) and TMSCl were added successively. 2-Fluorobenzoic acid (**1**) was again found to be present in similar quantities.

In order to suppress this side reaction, it is necessary for the coupling reagent to be in situ before addition of *n*-BuLi.[11] Accordingly, we were able to obtain the required silylated compound **7** in pure form by dissolving TMSCl and **10** in sodium-dried THF, cooling to −90°C, and then adding *n*-BuLi (entry 3). In the literature, similar results have been obtained for other aromatic compounds.[12]

A rather interesting and significant event occurred during this study. Deuterium was incorporated at the C6-position at a level of 30 % by adding *n*-BuLi to a flask containing **10** dissolved in sodium dried-THF, subsequently wetted with D_2O (entry 4). A maximal amount of deuterium incorporation of 52 % was obtained when a larger excess of *n*-BuLi (6 equiv.) and D_2O (8 equiv.) were used (entry 5). It follows that the Br-Li exchange/D_2O trapping sequence can compete successfully with the direct attack of D_2O by *n*-BuLi. In fact, this situation is not unique. Forty years ago, Taylor reported a convenient approach to synthesize 9-tritiated anthracene by addition of *n*-BuLi to a mixture of 9-bromoanthracene and T_2O in ether at −70°C, which implies that *n*-BuLi reacts with the bromoarene faster than with tritiated water.[12] More recently, Capriati et al. showed that directed *ortho*-lithiation of diaryltetrahydrofurans can compete successfully with protonolysis in protic eutectic solvent mixtures.[13,14]

The existence of a cluster or mixture of aggregates held together by non-covalent bonds (‘supramolecules’) could explain why *n*-BuLi does not react more effectively with water. Under certain conditions, water can act as an effective ligand for lithium, and the resulting ‘coordinated’ water exhibits a different reactivity from ‘free’ water. The organolithium species RLi and **10** being involved within aggregates by weak electrostatic interactions, the topology of the pocket might also be responsible for the reaction pathway observed after the electrophile penetrates the cluster.[15] The reluctance of water and its isotopes (D_2O and T_2O) to react with *n*-BuLi *at low temperatures* (~−80°C) casts doubt on reports regularly quoted in the scientific literature.[16]

Table 2. S_NAr reactions of 2-fluoro and 2-methoxy-6-(trimethylsilyl)benzoic acids (7) and (8)[A,B]



1 X = F, Y = H
7 X = F, Y = TMS
2 X = OMe, Y = H
8 X = OMe, Y = TMS

11 Y = H
12 Y = TMS

13 X = F, Y = H
14 X = F, Y = TMS
15 X = OMe, Y = H
16 X = OMe, Y = TMS

a R = *n*-Bu
b R = *s*-Bu
c R = *t*-Bu
d R = Ph
e R = 4-$MeOC_6H_4$
f R = 4-$Me_2NC_6H_4$

Entry	Acid	RM (2.2 equiv.), conditions[C]	**11**, **12**	**13–16**
1	**1**	*n*-BuLi, −78°C	0 (**11a**)	38 (**13a**)
2	**1**	*s*-BuLi, −78°C	58 (47*) (**11b**)	39 (**13b**)
3	**1**	*t*-BuLi, −78°C	68 (63*) (**11c**)	0
4	**1**	PhLi, −30°C → rt	17 (**11d**)	75 (**13d**)
5	**7**	*n*-BuLi, −78°C	70 (65*) (**12a**)	20 (**14a**)
6	**7**	*s*-BuLi, −78°C	88 (69*) (**12b**)	10 (7*) (**14b**)
7	**7**	*t*-BuLi, −78°C	80 (72*) (**12c**)	0
8	**7**	PhLi, −30°C → rt	60 (57*) (**12d**)	0
9	**7**	4-$MeOC_6H_4Li$, −30°C → rt	69 (50*) (**12e**)	0
10	**7**	4-$Me_2NC_6H_4Li$, −30°C → rt	60 (43*) (**12f**)	0
11	**7**	*n*-BuMgBr, 30°C	<5 (**12a**)	17 (**14a**)
12	**7**	PhMgBr, 30°C	<5 (**12d**)	17 (**14d**)
13	**2**	*s*-BuLi, −65°C	25 (**11b**)	45 (**15b**)
14	**2**	*t*-BuLi, −78°C → 0°C	39 (**11c**)	0
15	**8**	*n*-BuLi, −78°C	0	44 (**14a**)
16	**8**	*s*-BuLi, −78°C	36 (**12b**)	0
17	**8**	PhLi, −30°C → rt	38 (**12d**)	0

[A]Crude yields (%) estimated by ^1H NMR. Isolated yields are denoted by an asterisk (*).
[B]Entries 1–4, 13, 14: see refs.[2,3]
[C]RM denotes the nucleophile.

6-Silylated benzoic acids **7** and **8** were subjected to a series of organolithium and Grignard reagents (Table 2). The results obtained with the unsilylated benzoic acids **1** and **2** are also provided for comparison purposes. *n*-BuLi has the stronger nucleophilic character and the weaker complexing ability towards the carboxylate. The S_NAr/NA selectivity follows the order *n*-Bu < *s*-Bu < *t*-Bu when the corresponding alkyllithiums are allowed to react with 2-fluorobenzoic acid (**1**) (entries 1–3). Introduction of a TMS group in C6 shields effectively the carboxylate and suppresses in most cases the undesired nucleophilic addition (entries 5–7). In all cases studied, the S_NAr reaction proceeds smoothly and the aromatic ring is not lithiated at all. The method described provides excellent latitude with respect to the synthesis of biaryl compounds (compare entries 8–10 with entry 4).[17] The 2-methoxy derivative **8** is less reactive than its fluoro counterpart **7**.[18] Alkyl and aryl Grignard reagents are not effective for these transformations. Removal of the 'traceless' trialkylsilyl group can be accomplished with various sources of fluoride.[6]

It is by no means obvious to rationalize how a bulky substituent can shield a neighbouring carboxylate against nucleophilic attack so effectively. Although details are yet to be clarified, we propose the following reaction mechanism. At first sight, the obstruction of the nucleophilic attack at the carboxylate can be attributed to trivial steric hindrance caused by the bulky trialkylsilyl substituent.[6,19] Taking into account the fact that 2,6-disubstituted benzoate esters tetrahedral hydrolysis mechanisms are disfavoured over S_N1 or S_N2 processes,[20] lithium carboxylate would be resistant to NA, provided the carboxylate is orthogonal to the arene and attack is then sterically prevented. However, the carboxylate must be coplanar to the arene for the S_NAr. Consequently, the electronic effect associated with the silicon atom most likely plays the most important role. If it is assumed that the reaction proceeds via an addition–elimination sequence,[21] the carboxylate and the fluorine atom could initially provide a residence site for the lithium cation (complex-induced proximity effect process, CIPE) (Fig. 2).[22,23] The resulting complex **A′** allows the carboxylate to orientate itself with the aromatic ring in a coplanar fashion. The transition state leading to **B** may be envisioned as forming from **A′**, where the R group enters from the side almost perpendicular to the aromatic ring (to the π cloud). The ability of the silicon 3p orbitals to engage in electron-rich three-centre four-electron (3c-4e) bonding allows Si to expand its coordination sphere to a pentacoordinate silicon complex, and formation at a lower energy cost of a silalactone scaffold[24] in the resonance-stabilized Meisenheimer complex intermediate **B** must be envisaged.[25] Hypervalency could also originate from vacant d orbitals at silicon combined with the potential influence of σ* (Si–C/O) orbitals. However, these two theories are still a matter of debate.[25] The intramolecular coordination presumably accelerates the nucleophilic substitution rate. It is noteworthy

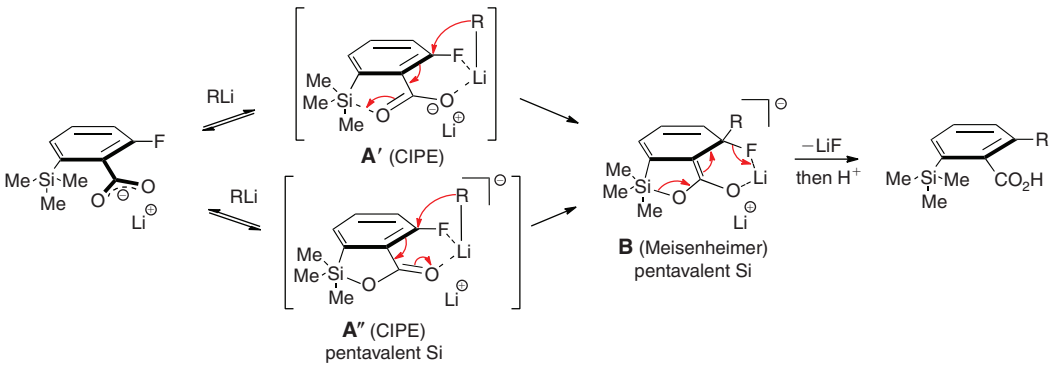


Fig. 2. Plausible reaction mechanism.

that cyclization leading to the silalactone complex **A″** might precede complexation with RLi.

In the literature, coupling reactions between polar organometallic reagents and halo or alkoxybenzenes are most frequently carried out using transition metal catalysts and aryl halides.[26] In the pharmaceutical industry, these reactions have major shortcomings. Because the limits set by health authorities are very low,[27] the effective removal of transition metals (e.g. Pd, Cu) in active pharmaceutical ingredients (API) continues to be a challenge. When the synthetic scheme of an industrial process requires the use of a metal of significant safety concern and that the standards of metal content permitted in the API are exceeded, it is generally necessary to find empirically a disposal method such as nanofiltration or use of scavenging agents, which is costly in time and money.[28]

In contrast, silicon is considered to be an element of a relatively low order of toxicity.[29]

Direct (uncatalyzed) coupling of Grignard or lithium reagents is rarely successful although exceptions are known. In the Meyers reaction,[30] 2-fluoro- and 2-methoxyaryl oxazolines react with Grignard, organolithium reagents, and lithio amides usually around −20°C, furnishing the substituted aromatics. This reaction has been used for the synthesis of a variety of natural products and in some cases, this direct approach has proved superior to transition metal-catalyzed approaches.[31] Miyano et al. reported that esters and sulfonyl substituents can take the place of the oxazolinyl group to give similar chelation-assisted S_NAr reactions.[19] Nevertheless, these transformations require laborious protection and deprotection steps to restore the carboxylic acid moiety. Deprotection of aryloxazolines requires the use of acidic conditions (3 M HCl, 12–24 h, reflux), which are not compatible with delicate structures.[30] Furthermore, 2,6-disubstituted aryloxazolines, benzoate esters, and benzamides are inert to hydrolysis except in cases where anchimeric assistance by *ortho*-introduced electrophiles can give five- or six-membered ring tetrahedral intermediates, which greatly enhances hydrolytic rates.[32]

Conclusion

To the best of our knowledge, alkyl and aryl organolithium displacement of an *ortho*-fluoro group from unprotected benzoic acids is unprecedented. This facile process, which occurs under unexpectedly mild conditions (−78–40°C, THF), possesses considerable potential and opens a route to asymmetrically substituted biaryls.[33] Unprecedented is the finding that a TMS group shields the carboxylate against nucleophilic attack, thus reducing dramatically the formation of ketones, and reorients the nucleophilic substitution to the 2-position.

Experimental

Materials and Measurements

All experiments were carried out under argon with anhydrous THF in dried glassware, using syringe-septum cap techniques. For standard working practice, see ref.[34] THF was purchased from Aldrich and dried using the drying station GT S100 (Glass Technology). *n*-BuLi and *s*-BuLi were purchased from Acros Chemicals and Aldrich Chemical Co. as solutions in hexane and cyclohexane, respectively, and were titrated periodically against *N*-benzylbenzamide.[35] Flash column chromatography was carried out using Merck Kieselgel 60 silica gel (particle size: 32–63). Analytical TLC was performed using Merck pre-coated silica gel 60 F-254 sheets. ^{1}H 200 MHz, ^{1}H 400 MHz, ^{13}C 50 MHz, ^{13}C 100 MHz, and ^{19}F 376 MHz NMR spectra were recorded on a Bruker DPX 200 spectrometer or a Bruker AC-400 spectrometer. Infrared (IR) spectra were recorded neat or as thin films using a Nicolet Avatar 370 DTGS Fourier transform infrared (FT-IR) spectrometer. High-resolution mass spectroscopy (HRMS) was conducted on a Micromass GCT Premier. Melting points were measured on a Büchi Melting Point B-540 apparatus and are uncorrected. Elemental analyses were performed by the *Service de Microanalyse*, CNRS ICSN, Gif-sur-Yvette (France).

*Preparation of 2-Fluoro-6-trimethylsilylbenzoic Acid (**7**)*

*6-Bromo-2-fluorobenzoic Acid (**10**)*

Adapted from a literature procedure.[36] To a flask containing anhydrous diisopropylamine (9.24 mL, 66 mmol) in dry THF (300 mL) at −30°C, *n*-BuLi (1.6 M in hexane, 41.3 mL, 66 mmol) was added dropwise. The mixture was then cooled to −78°C, and 3-bromofluorobenzene (**9**) (6.6 mL, 60 mmol) was slowly added. After 2 h of reaction at this temperature, the reaction mixture was quenched with dry ice. Stirring was maintained for 3 h, and the mixture was then slowly allowed to warm to room temperature (rt), and hydrolyzed with water (300 mL). The aqueous layer was washed with ether (2 × 150 mL), acidified with 2 M HCl (pH 1–2), and extracted with ether (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the residue by recrystallization (cyclohexane/ethylacetate) afforded 6-bromo-2-fluorobenzoic acid (**10**) as a white solid (11.8 g, 90 %), mp 154–155°C (lit. 152–154°C[37]).

ν_{max} (neat)/cm^{-1} 2872, 2665, 1696, 1600, 1449, 1297. δ_H ($CDCl_3$, 400 MHz) 7.45 (1H, d, *J* 8.1), 7.32 (1H, dt, *J* 8.4, 5.8), 7.14 (1H, dd, *J* 9.4, 1.1). δ_C (100 MHz, [D6]DMSO) 164.6, 158.2 (d, *J* 250.0), 132.1 (d, *J* 8.9), 128.6, 125.7 (d, *J* 22.0), 118.6 (d, *J* 5.1), 115.1 (d, *J* 21.2).

*2-Fluoro-6-trimethylsilylbenzoic Acid (**7**)*

The synthesis of 2-fluoro-6-trimethylsilylbenzoic acid (**7**) under EQ conditions (Table 1, entry 2) is described as follows.

n-BuLi (1.6 M in hexane, 26 mL, 41 mmol) was added dropwise to a solution of 2-fluoro-6-bromobenzoic acid (**10**) (4.38 g, 20 mmol) in dry THF (120 mL) at −90°C. The mixture was stirred for 2 h, and TMSCl (9.2 mL, 70 mmol) was added. The solution was hydrolyzed with 1 M NaOH (pH 10–11), and the aqueous layer was washed with ether (2 × 50 mL) and acidified with 2 M HCl (pH 1–2). After extraction of the aqueous layer with ether (3 × 60 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give a sticky residue containing 2-fluoro-6-trimethylsilylbenzoic acid (**7**) (82 % yield) and 2-fluorobenzoic acid (10 % yield) (the yields were estimated by ^{1}H NMR analysis). 2-Fluoro-6-trimethylsilylbenzoic acid (**7**) was separated by chromatography on silica gel (hexane/ether 90 : 10) as a white solid (2.0 g, 47 %), mp 88.4–89°C. ν_{max} (neat)/cm^{-1} 2957, 2654, 1686, 1464, 1291, 1236. δ_H ($CDCl_3$, 400 MHz) 7.47–7.52 (2H, m), 7.14 (1H, m), 0.34 (9H, s). δ_C ($CDCl_3$, 50 MHz) 172.8, 161.0 (d, *J* 258.0), 144.1, 132.6 (d, *J* 8.1), 130.6, 124.1 (d, *J* 10.6), 117.0 (d, *J* 22.3), 0.54.

The synthesis of 2-fluoro-6-trimethylsilylbenzoic acid (**7**) under ISQ conditions (Table 1, entry 3) is described as follows.

To a flask containing a stirred solution of 2-fluoro-6-bromobenzoic acid (**10**) (0.876 g, 4 mmol) in dry THF (24 mL) at −90°C under argon, TMSCl (2.24 mL, 16 mmol) and *n*-BuLi (1.6 M in hexane, 6.25 mL, 10 mmol) were added successively The mixture was slowly allowed to warm to rt over a period of 6 h, and hydrolyzed with water (20 mL). Then, 1 M NaOH was added (pH 9–10). The aqueous layer was washed with ether (2 × 30 mL), acidified with 1 M HCl (pH 1–2), and the aqueous phase was extracted with ether (3 × 30 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated under vacuum. Compound **7** was purified by filtration on silica gel and recrystallized (hexane/toluene) as a white solid (0.46 g, 54 %), mp 88.4–89°C.

*2-Methoxy-6-trimethylsilylbenzoic Acid (**8**)*

To a solution of LTMP (9 mmol) in THF (20 mL) at −78°C, TMSCl (1.38 mL, 10.5 mmol) in THF (5 mL) and 2-methoxybenzoic acid (**2**) (0.46 g, 3 mmol) in THF (3 mL) were added successively. After gradual warming of the reaction mixture to rt over a period of 4 h, aqueous 2 M NaOH was added until the pH reached 10. The aqueous layer was washed with ether, acidified with aqueous 4 M HCl, and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (cyclohexane/ether 90 : 10) to give 2-methoxy-6-trimethylsilylbenzoic acid (**8**) as a white solid (0.60 g, 89 %), mp 85.5–87.0°C.[2] δ_H ($CDCl_3$, 200 MHz) 0.33 (9H, s), 3.98 (3H, s), 7.05 (1H, d, *J* 8.4), 7.37 (1H, d, *J* 7.8), 7.51 (1H, dd, *J* 8.4, 7.8). δ_C ($CDCl_3$, 100 MHz) 0.6 (3C), 56.0, 112.1, 124.2, 127.9, 131.8, 144.4, 157.2, 170.3. ν_{max} (neat)/cm^{-1} 2840, 1681, 1571, 1445, 1243, 1126, 950. Anal. Calcd. for $C_{11}H_{16}O_3Si$: C 58.89, H 7.19. Found: C 58.94, H 7.12 %.

*6-Deutero-2-fluorobenzoic Acid (**1**-6d$_1$) (Table 1, Entry 5)*

To a solution of 2-fluoro-6-bromobenzoic acid (**10**) (0.423 g, 3 mmol) and D_2O (0.43 mL, 24 mmol) in dry THF (18 mL) at −90°C, *n*-BuLi (1.6 M in hexane, 18 mmol) was added dropwise. After stirring of the reaction mixture at this temperature for 2 h, the reaction mixture was allowed to warm to rt over a period of 6 h, and hydrolyzed with water (30 mL). The aqueous layer was washed with ether (2 × 30 mL), acidified with 2 M HCl (pH 1–2), and extracted with ether (3 × 30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude yield (52 %) was estimated by ^{1}H NMR spectroscopy. δ_H ($CDCl_3$, 200 MHz) 7.61 (1H, m), 7.13–7.31 (2H, m).

*Nucleophilic Aromatic Substitution Reactions of 2-Fluoro-6-trimethylsilylbenzoic Acid (**7**) and 2-Methoxy-6-trimethylsilylbenzoic Acid (**8**)*

General Procedure Involving Alkyllithium Nucleophiles

The alkyllithium (10.5 mol) was added dropwise to a solution of **7** or **8** (5 mmol) in dry THF (20 mL) at −78°C under argon. After 2 h of stirring, the reaction mixture was allowed to warm to rt, and hydrolyzed with water (30 mL). The aqueous layer was washed with ether (2 × 30 mL). The aqueous layer was acidified with 1 M HCl (pH 1–2), and extracted with ether (3 × 30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum to give the *ipso*-substitution product, which was purified by chromatography.

*2-n-Butyl-6-trimethylsilylbenzoic Acid (**12a**) (Table 2, Entry 5)*

Compound **12a** was obtained according to the general procedure from 2-fluoro-6-trimethylsilylbenzoic acid (**7**) (0.424 g, 2 mmol) and *n*-BuLi (2 M in hexane, 2.2 mL, 4.4 mmol). Chromatography on silica gel (cyclohexane/diethylether 90 : 10) gave **12a** as a white solid (0.331 g, 65 %), mp 76–77.8°C. δ_H ($CDCl_3$, 400 MHz) 7.46 (1H, dd, *J* 7.2, 1.6), 7.36 (1H, t, *J* 7.2), 7.28 (1H, dd, *J* 7.6, *J* 1.5), 2.76 (2H, m), 1.73–1.56 (2H, m), 1.49–1.31 (2H, m), 0.94 (3H, t, *J* 7.2), 0.34 (9H, s).

*2-s-Butyl-6-trimethylsilylbenzoic Acid (**12b**) (Table 2, Entry 6)*

Compound **12b** was obtained according to the general procedure from 2-fluoro-6-trimethylsilylbenzoic acid (**7**) (1.19 g, 4.77 mmol) and *s*-BuLi (1.3 M in hexane, 8.1 mL, 10.5 mmol). Chromatography on silica gel (cyclohexane/ethylacetate 90 : 10) afforded **12b** as a colourless oil (69 % yield). ν_{max} (neat)/cm^{-1} 2961, 2650, 1686, 1457, 1285, 1246. δ_H ($CDCl_3$, 400 MHz) 7.44 (1H, dd, *J* 7.4, 1.5), 7.40 (1H, t, *J* 7.6), 7.33 (1H, dd, *J* 7.6, 1.5), 2.93 (1H, m), 1.76–1.56 (2H, m), 1.27 (3H, d, *J* 6.8), 0.85 (3H, t, *J* 7.6), 0.35 (9H, s). δ_C ($CDCl_3$, 100 MHz) 177.9, 174.5, 144.3, 137.6, 132.2, 129.5, 126.7, 38.1, 31.2, 22.2, 12.3, −0.6. HRMS *m*/*z* 250.1395; calcd for $C_{14}H_{22}O_2Si$ ($[M]^+$) 250.1389.

*2-t-Butyl-6-trimethylsilylbenzoic Acid (**12c**) (Table 2, Entry 7)*

Compound **12c** was obtained according to the general procedure from 2-fluoro-6-trimethylsilylbenzoic acid (**7**) (1.19 g, 4.77 mmol) and *t*-BuLi (1.6 M in hexane, 6.6 mL, 10.5 mmol). Chromatography on silica gel (cyclohexane/ethylacetate 90 : 10) afforded **12c** as a white solid (72 % yield), mp 163–165°C. ν_{max} (neat)/cm^{-1} 2960, 2637, 1688, 1287, 1244, 1103. δ_H ($CDCl_3$, 400 MHz) 7.54 (1H, dd, *J* 8.0, 1.3), 7.47 (1H,

dd, *J* 7.3, 1.1), 7.36 (1H, dd, *J* 7.8, 7.6), 1.48 (9H, s), 0.35 (9H, s). δ_C ($CDCl_3$, 100 MHz) 179.8, 146.2, 137.8, 136.9, 132.4, 128.9, 127.5, 36.2, 31.5, −0.6. HRMS *m/z* 250.1387; calcd for $C_{14}H_{22}O_2Si$ ($[M]^+$) 250.1389. Anal. Calc. for $C_{14}H_{22}O_2Si$: C 67.15, H 8.86. Found: C 66.86, H 8.58 %.

General Procedure Involving Aryllithium Nucleophiles

At −78°C, *n*-BuLi (4.13 mL, 6.6 mmol, 1.6 M in hexane) was added slowly to a solution of arylbromide (6.6 mmol) in dry THF (12 mL). After 1 h of stirring, the mixture was allowed to warm to −50°C, and the acid (**7** or **8**) (3 mmol) in THF (4 mL) was added. The mixture was stirred at rt for 24 h (for **7**) or refluxed for the same period (for **8**). Water (30 mL) was added, and the aqueous layer was washed with ether (2 × 30 mL) and acidified with 1 M HCl (pH 1–2). After extraction of the aqueous layer with ether (3 × 30 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to give the *ipso*-substitution products **12d**–**f**, which were purified by chromatography or recrystallization.

*3-(Trimethylsilyl)biphenyl-2-carboxylic Acid (**12d**) (Table 2, Entry 8)*

Compound **12d** was obtained according to the general procedure from bromobenzene (1.04 g, 0.7 mL, 6.6 mmol), *n*-BuLi (4.13 mL, 6.6 mmol, 1.6 M in hexane), and 2-fluoro-6-(trimethylsilyl)benzoic acid (**7**) (0.64 g, 3 mmol). Recrystallization (cyclohexane) gave **12d** as a white solid (0.46 g, 57 %), mp 146–148°C. This compound can also be prepared by metalation/silylation of biphenyl-2-carboxylic acid.[38] ν_{max} (neat)/cm^{-1} 2957, 2558, 1685, 1427, 1299, 1249, 1135. δ_H ($CDCl_3$, 400 MHz) 7.60 (1H, dd, *J* 7.4, 1.3), 7.47 (1H, t, *J* 7.6), 7.40–7.36 (5H, m), 0.38 (9H, s). δ_C ($CDCl_3$, 100 MHz) 177.6, 140.9, 140.1, 138.7, 133.6, 130.8, 129.4, 128.5, 128.4, 127.5, −0.6. HRMS *m/z* 270.1078; calcd for $C_{16}H_{18}O_2Si$ ($[M]^+$) 270.1076. Anal. Calc. for $C_{16}H_{18}O_2Si$: C 71.07, H 6.71. Found: C 71.11, H 6.81 %.

*2-(4-Methoxyphenyl)-6-trimethylsilylbenzoic Acid (**12e**) (Table 2, Entry 9)*

Compound **12e** was obtained according to the general procedure from 4-methoxy-1-bromobenzene (1.24 g, 0.83 mL, 6.6 mmol), *n*-BuLi (4.13 mL, 6.6 mmol, 1.6 M in hexane), and 2-fluoro-6-(trimethylsilyl)benzoic acid (**7**) (0.64 g, 3 mmol). Chromatography (hexane/ethylacetate 90 : 10) gave **12e** as a white solid (0.45 g, 50 %), mp 164–166°C. ν_{max} (neat)/cm^{-1} 2958, 2639, 1683, 1513, 1299, 1240. δ_H ($CDCl_3$, 400 MHz) 7.56 (1H, dd, *J* 7.6, 1.3), 7.43 (1H, t, *J* 7.6), 7.35 (1H, dd, *J* 7.8, 1.3), 7.31 (2H, d, *J* 8.8), 6.90 (2H, d, *J* 8.8), 3.83 (3H, s), 0.38 (9H, s). δ_C ($CDCl_3$, 100 MHz) 177.6, 159.2, 139.7, 138.6, 137.1, 133.3, 130.8, 129.5, 113.9, 55.3, −0.6.

*2-(4-Dimethylaminophenyl)-6-trimethylsilylbenzoic Acid (**12f**) (Table 2, Entry 10)*

Compound **12f** was obtained according to the general procedure from 4-dimethylamino-1-bromobenzene (1.32 g, 6.6 mmol), *n*-BuLi (4.13 mL, 6.6 mmol, 1.6 M in hexane), and 2-fluoro-6-(trimethylsilyl)benzoic acid (**7**) (0.64 g, 3 mmol). Recrystallization (cyclohexane/ethylacetate 90 : 10) gave **12f** as a white solid (0.404 g, 43 %), mp 182–184°C. ν_{max} (neat)/cm^{-1} 2955, 2558, 1692, 1609, 1521, 1285, 1250. δ_H ($CDCl_3$, 400 MHz) 7.53 (1H, dd, *J* 7.6, 1.5), 7.42 (1H, t, *J* 7.6), 7.39 (1H, dd, *J* 7.8, 1.3), 7.30 (2H, d, *J* 8.8), 6.71 (2H, d, *J* 8.8), 2.83 (6H, s), 0.38 (9H, s). δ_C ($CDCl_3$, 100 MHz) 176.8, 149.7, 139.8, 138.3, 137.5, 132.7, 131.0, 129.1, 113.4, 41.0, −0.6.

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