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First General, Direct, and Regioselective Synthesis of Substituted Methoxybenzoic Acids by Ortho Metalation

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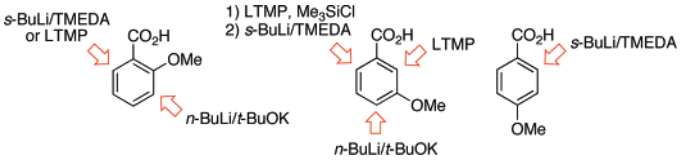

New general methodology of value in aromatic chemistry based on ortho-metalation sites in *o*-, *m*-, and *p*-anisic acids (**1**−**3**) (Scheme 1) is described. The metalation can be selectively directed to either of the ortho positions by varying the base, metalation temperature, and exposure times. Metalation of *o*-anisic acid (**1**) with *s*-BuLi/TMEDA in THF at −78 °C occurs exclusively in the position adjacente to the carboxylate. On the other hand, a reversal of regioselectivity is observed with *n*-BuLi/*t*-BuOK. With LTMP at 0 °C, the two directors of *m*-anisic acid (**2**) function in concert to direct introduction of the metal between them while *n*-BuLi/*t*-BuOK removes preferentially the proton located ortho to the methoxy and para to the carboxylate (H-4). *s*-BuLi/TMEDA reacts with *p*-anisic acid (**3**) exclusively in the vicinity of the carboxylate. According to these methodologies, routes to very simple methoxybenzoic acids with a variety of functionalities that are not easily accessible by other means have been developed (Table 1).

Introduction

There are a number of carboxylic acid derivatives such as secondary and tertiary amides, esters, α-amino alkoxides, oxazolines, acetals, imidazolidines, imidazoles, and cyclohexylimines which are widely used for directed ortho-metalation (DoM).[1] The advantages of the tertiary amide directing metalation group (DMG), originally introduced by Beak in 1977,[2] include ease of preparation, priority over directors during the metalation step, utility in polysubstituted aromatic systems, and resistance to nucleophilic attack. The resistance to nucleophilic attack can be a problem if one wishes to convert the tertiary amide group into another functionality. In fact, the main disadvantages of *N*,*N*-dialkylamides as DMGs are their resistance to hydrolysis[1,2] and the paucity of methods for their transformation to other useful functionalities. Comins and Brown[3] and Reitz and Massey[4] have addressed the hydrolysis problem by developing *tert*-amide DMGs which are readily converted into secondary amides, the cleavage of which, via the *N*-nitrosoamide, has long been known. Snieckus et al.[5] have shown that *N*-methyl-*N*-[bis(trimethylsilyl)methyl]benzamides and their monotrimethylsilyl analogues are ortho-lithiated and that the derived ortho-substituted products can be transformed, in two steps, into the corresponding benzyl alcohols or benzaldehydes.

The use of β-amino tertiary amides in place of the *N*,*N*-dialkylamide allows for more versatility in manipulating the directing group after ortho substitution has been effected.[3] However, deprotection of the amide group still requires drastic conditions, typically 6 N HCl hydrolysis or three-step, one-pot reaction involving methylation, elimination, and treatment with aqueous acid,[4] which are very often not applicable for delicate

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TABLE 1. Regioselective Preparation of Substituted *o*-, *m*-, and *p*-Anisic Acids[a]

starting acid	lithiation condition[b]	electrophile	E	product	% (isolated)	mp (°C)	mp (°C, lit.)
1	A	MeI	6-Me	**4a**	61	138.5−139	137−138 [4]
1	A[c]	TMSCl	6-Me_3Si	**4b**	89	85.5−87	−
1	A	C_2Cl_6	6-Cl	**4c**	58	142.5−144	140−141[26]
1	A	$C_2Br_2Cl_4$	6-Br	**4d**	59	127−129	124−127[22g]
1	A	I_2	6-I	**4e**	46	129−131	128−130[27]
1	A	Me_2S_2	6-MeS	**4f**	47	182−184	184−185[28]
1	A[d]	DMF	6-CHO	**4g**[e]	43	155−157	155−156[29]
1	A[d]	PhCHO	6-PhCH(OH)	**4h**[f]	52	136−138	139−141.5[30]
1	A[d]	$BrCH_2CH{=}CH_2$	6-$CH_2CH{=}CH_2$	**4i**	45	89−91	91[31]
1	A[d]	$BrCH_2Ph$	6-CH_2Ph	**4j**	47	148−149.5	−
1	B	MeI	3-Me	**5a**	40	81−83	83−83.5[3 2]
1	B	TMSCl	3-Me_3Si	**5b**	40	96−98	−
1	B	C_2Cl_6	3-Cl	**5c**	39	114−116	−
1	B[d]	$C_2Br_2Cl_4$	3-Br	**5d**	34	119−121	121[33]
1	B[d]	I_2	3-I	**5e**	27	122−124	−
1	B	Me_2S_2	3-MeS	**5f**	45	77−79	−
1	B[d]	PhCHO	3-PhCH(OH)	**5g**	41	124−126	−
2	C[d]	MeI	2-Me	**6a**	50	145−146	146.5−149[34]
2	C[c,g]	TMSCl	2-Me_3Si	**6b**	75	91−92	−
2	C	C_2Cl_6	2-Cl	**6c**	47	160−161	−
2	C	$C_2Br_2Cl_4$	2-Br	**6d**	60	154−155	155−156[35]
2	C	I_2	2-I	**6e**	53	145−146	148−149[36]
2	C	Me_2S_2	2-MeS	**6f**	46	132−134	−
2	C	DMF	2-CHO	**6g**[h]	27	154−155	156−157[37]
2	C	PhCHO	2-PhCH(OH)	**6h**[i]	65	147−148	−
2	C	O_2	2-OH	**6i**	54	150−152	151[38]
2	D	MeI	4-Me	**7a**	59	210−213	212−214[21b]
2	D	C_2Cl_6	4-Cl	**7b**	39	210−212	−
2	D	$C_2Br_2Cl_4$	4-Br	**7c**	45	212−213	−
2	D	I_2	4-I	**7d**	20	210−212	−
2	D	Me_2S_2	4-MeS	**7e**	51	186−187	−
2	D	PhCHO	4-PhCH(OH)	**7f**	54	122−124	−
2	E	MeI	6-Me	**8a**	54	151−152	151−151.5[39]
2	E	C_2Cl_6	6-Cl	**8b**	55	168−169.5	169−171[40]
2	E	$C_2Br_2Cl_4$	6-Br	**8c**	63	158−160	160[41]
2	E	I_2	6-I	**8d**	50	132.5−134	−
2	E	MeI	6-MeS	**8e**	61	144−146	−
3	F	MeI	2-Me	**9a**	73	177−178.5	176−178[42]
3	F[c]	TMSCl	2-Me_3Si	**9b**	80	134−136.5	−
3	F	C_2Cl_6	2-Cl	**9c**	75	111.5−113	−
3	F	$C_2Br_2Cl_4$	2-Br	**9d**[j]	54	−	−
3	F	I_2	2-I	**9e**	71	173−175	−
3	F	Me_2S_2	2-MeS	**9f**	76	118−120	−
3	F	DMF	2-CHO	**9g**[k]	64	134−136	−
3	F	PhCHO	2-PhCH(OH)	**9h**[l]	69	124−126	−

[a] Analytical and spectra data (IR, NMR, MS) data are in accord with the structures of all new compounds. For general procedures, see Experimental Section. [b] External quench except otherwise noted. [c] *In situ* quench technique. See Experimental Section. [d] Reverse addition. See ref 50. [e] Product cyclized into 3-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one (**11**). [f] Product cyclized into 7-methoxy-3-phenylisobenzofuran-1(3*H*)-one (**12**). [g] 3-Methoxy-2,6-bis(trimethylsilyl)benzoic acid (**10**) resulting from the partial deprotonation of lithium salt of the primary product **6b** by the excess of base at the carbon C-6 was also isolated (7%). [h] Product cyclized into 3-hydroxy-4-methoxyisobenzofuran-1(3*H*)-one (**13**). [i] Products cyclized into 4-methoxy-3-phenylisobenzofuran-1(3*H*)-one (**14**). [j] Two isomers **9d** and **20** (**9d/20**, 48:52) could not be separated by chromatography. [k] Product cyclized into 3-hydroxy-5-methoxyisobenzofuran-1(3*H*)-one (**15**). [l] Product cyclized into 5-methoxy-3-phenylisobenzofuran-1(3*H*)-one (**16**).

structures. Secondary benzamides, although useful in directed metalation syntheses usually suffer from problems which arise from the lack of solubility of the dianion generated.[6] Many times their reactions require the use of a cosolvent (e.g., HMPA) and/or higher reaction temperatures which sometimes cause unwanted side reactions.[7,8]

The best protecting group is the one which can be omitted. When the carboxylic acid substituent is employed as a DMG, substantial selectivity toward metalation can be obtained.[9] This group increases the discrimination between ortho positions, and favors metalation over nucleophilic addition reactions to the aromatic nucleus.[10] Herein we detail our investigations on the synthetic utility of the CO_2Li group for the preparation of *o*-, *m*-, and *p*-anisic acids substituted with a variety of functionalities. The CO_2Li DMG is of modest strength when compared to some of the strong ortho-directors, but it is strong enough to exert a substantial directing influence in the presence of a MeO group. More importantly, the carboxylic acid group permits a

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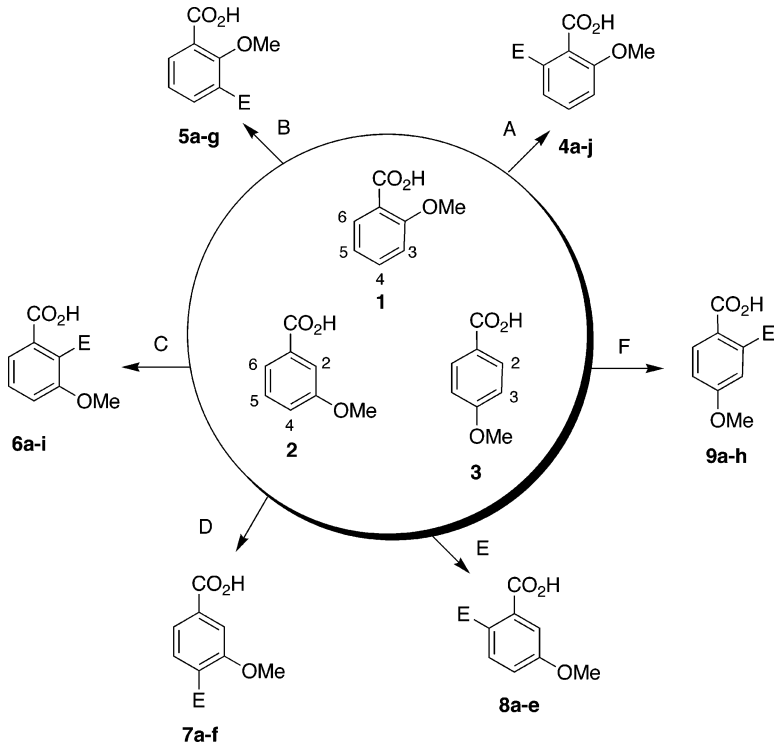
SCHEME 1[a]



[a] A: (1) *s*-BuLi/TMEDA (1:1, 2.2 equiv), THF, −78 °C, 2 h; (2) EX, −78 °C; (3) 2 M HCl, rt. B: (1) *n*-BuLi/*t*-BuOK (1:1, 4 equiv), THF, −78 °C, 2 h; (2) EX, −78 °C; (3) 2 M HCl, rt. C: (1) LTMP (5 equiv), THF, 0 °C; (2) EX, 0 °C, 40−65 °C; (3) 2 M HCl, rt. D: (1) *n*-BuLi/*t*-BuOK (1:1, 4 equiv), THF, −78 °C → −50 °C; 2) EX, −50 °C; (3) 2 M HCl, rt. E: (1) LTMP (5 equiv), TMSCl, 75% of **6b**; (2) *s*-BuLi/TMEDA (4 equiv), THF, −78 °C → −30 °C; (3) EX, −30 °C; (4) 6 M HCl, rt. F: (1) *s*-BuLi/TMEDA, 2.2 equiv, THF, −78 °C, 2 h; (2) Ex, −78 °C; 3) 2 M HCl, rt.

remarkable degree of control of the regioselectivity of metalation between nonequivalent ortho centers.

Results and Discussion

Metalation regioselectivity is influenced by additives[11] and by variation of metalating agent.[12] *O*-anisic acid (**1**) when treated with *s*-BuLi/TMEDA (1:1, 2.2 equiv, THF, −78 °C, 2 h) followed by addition of an electrophile afforded only benzoic acids **4** substituted at the position ortho to the carboxylate (route A, Scheme 1).[13] DoM involving alkyllithiums is a prime example of a reaction that requires self-assembly before the transition state can be accessed. Since regioisomers **5** arising out of metalation ortho to the methoxy are not produced, *s*-BuLi approaches preferentially the benzoate **1** by chelation with the highly electron-rich π-system in the carboxylate (CIPE effect).[14] The resulting complex forces the deprotonation to occur into the ortho position leading to the lithiated species 6Li-**1** (see Figure 1) and ultimately the substitution products after reaction with the electrophile. The directing and accelerating effect of the carboxylate is probably due to the stabilization of *both* the initial complex and the transition structure whose geometries could be radically different.[15] The coordination becomes stronger in the transition state than in the initial complex. As a result,

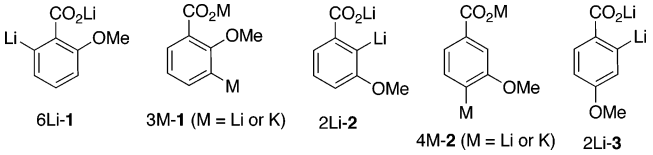


FIGURE 1. Dianions derived from anisic acids **1**−**3**.

complexation might increase the rate of reaction by providing a new mechanism that has a smaller activation energy.[16]

Lithium 2,2,6,6-tetramethylpiperidide (LTMP)[17] metalated **1** quantitatively in the position C-6 when *in situ* quench conditions were used (*vide infra*). These results strongly suggest that 6Li-**1** is formed under both kinetic and thermodynamic conditions. The trend is reversed by use of preformed LICKOR superbase[18] made of equimolecular amounts of *n*-BuLi and *t*-BuOK at −78 °C, furnishing 3-substituted-2-methoxybenzoic acids **5** via the dianion 3M-**1** (route B). The use of 4 equiv of base constitutes the best conditions investigated to date. *t*-BuOK is a strong ligand that is able to break up the ordinary tight tetrameric aggregates of *n*-BuLi to dimers or even monomers. The intramolecular solvation is no longer competitive under these circumstances and superbases preferentially attack the

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inductively activated aromatic position next to the most electronegative heteroatom and/or the most acidic position available.[19]

Under conditions of thermodynamic control, LTMP (5 equiv) deprotonated the isomeric *m*-anisic acid (**2**) at the doubly activated C-2-position (route C), affording lithium 2-lithio-3-methoxybenzoate (2Li-**2**) which was found to be indefinitely stable in the interval of temperature 0−60 °C.[16,20] The presence of a MeO group located meta to the carboxylate imparts a great deal of stability to this system relative to other benzoates.[21] To react efficiently with weak electrophiles, 2Li-**2** has to be heated up in refluxing THF (65 °C). When subjected to LICKOR (4 equiv), 4M-**2** formed preferentially (route D). To prepare the 6-substituted benzoates **8**, one had to block the C-2 site of **2** by introducing a trimethylsilyl group, lithiate again, deliver the electrophile, and remove the protecting group (route E). Although *s*-BuLi/TMEDA (2.2 equiv) reacted with *p*-anisic acid (**3**) exclusively at C-2 to give 2Li-**3** (route F), attempts to metalate the C-3 position failed.

Substituted anisic acids **4**−**9** are versatile starting materials for organic synthesis. Examination of ortho isomer **1** was performed because of the potential utility of regioselective metalations as routes to series of relatively inaccessible 3- and 6-substituted 2-hydroxybenzenes **4** and **5** which are characteristic features of many biologically active natural products of polyketide origin (macrolides, polyene antibiotics, tetracyclines, etc.).[22] Consideration of our tactic in the context of 2-, 4-, and 6-substituted-3-hydroxybenzoyl fragments **6**−**8** is useful in view of the large number of derived natural products that incorporate these substitution patterns.[23] Published routes reveal that these substitution patterns are not easily established.[24] Most of the previously known compounds were synthesized by tedious and largely inefficient classical multistep sequences.[25]

By employing the optimized conditions described above (routes A−F), a rich variety of substituted anisic acids **4**−**9** that are not easily accessible by conventional means were synthesized (Table 1). Although yields are only fair, they are usable, since no protection and deprotection steps of the DMG are needed. After standard workup (see Experimental Section), benzoic acids **4**−**9** were purified by recrystallization or chromatography for characterization in each case. With *n*-BuLi/*t*-BuOK (routes B and D), the metalation is not regiospecific; however, the major isomer is always readily isolated by fractional crystallization.

Several aspects of the data in Table 1 require emphasis. Methylation led to **4**−**9a** in acceptable purified yields.[43] Sequential reaction of **1** with 2.2 equiv of *s*-BuLi/TMEDA, 4 equiv of MeI, and excess aq. 2 M HCl gave 2-methoxy-6-methylbenzoic acid (**4a**) in 61% yield. Narashimhan[44] and Fisher[8] have shown that lithiation of *N*-methyl and *N*-propenyl-2-methoxybenzamides with *n*-BuLi (2 equiv) at −70 °C followed by reaction with MeI gave complex mixtures of products. It is also worthy of note that 2-methoxyphenyloxazolines react with organometallics (RLi, RMgX) not by metalation but by direct substitution of the methoxyl group, furnishing *o*-alkyl or *o*-aryl derivatives.[45] The fact that *N*,*N*-dialkyl-2-methoxybenzamides are metalated exclusively at the position adjacent to the amide illustrates the dominance of the tertiary

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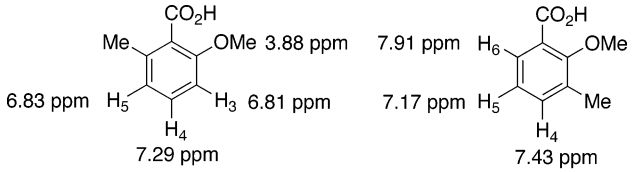


FIGURE 2. Structure determination of **4a** and **5a** by the NOESY technique.

amide groups in determining the position of lithiation;[46] however, the 2,6-disubstituted benzamides thus produced are inert to hydrolysis.[1a,47] Furthermore the regioisomers **5** are not accessible according to these methods.

Whereas 3-methoxyphenyloxazolines on treatment with either *n*-BuLi or *s*-BuLi/TMEDA gave mixtures of both the ortho- and para-products,[48] route C led to 3-methoxy-2-methylbenzoic acid (**6a**) as a sole isomer (45%) along with 2-ethyl-3-methoxybenzoic acid arising out of lateral metalation of **6a** (15%).[49] Thus, *even above 0 °C*, iodomethane in excess does not destroy totally the remaining LTMP which can then further deprotonate **6a** lithium salt. By slow addition of the preformed anion 2Li-**2** to a THF solution of MeI (reverse addition),[50] **6a** was produced in satisfactory yield (50%) while formation of 2-ethyl-3-methoxybenzoic acid was reduced to <3%.

The different sets of spatial interactions between different protons indicated by the NOESY technique help to establish the position of the methyl group of **4a** and **5a (**Figure 2). The hydrogen H_4 (7.29 ppm) of **4a** shows spatial interactions with H_3 (6.81 ppm) as well as with H_5 (6.83 ppm). Furthermore, the methoxy group (3.88 ppm) interacts with H_3 and the methyl group interacts with H_5. Therefore the methyl group of **4a** is located at the position adjacent to the carboxylate. The Me group of **5a** shows spatial interactions with H_4 (7.43 ppm); there are also interactions between H_4-H_5 (7.17 ppm) and H_5-H_6 (7.91 ppm), what is only possible if the methyl group is located in the neighborhood to the methoxy group. All compounds **6a**−**g** obtained as the result of lithiation of **2** at the position C-2, ortho to both substituents, show a characteristic triplet corresponding to the H-5 proton in the ^{1}H NMR spectra. The products of lithiation ortho to the methoxy group and para to the carboxylate (**7a**−**f**) exhibit a characteristic doublet for H-5. The site of lithiation and subsequent electrophilic addition is also confirmed by the melting points of the previously known compounds with the literature values.

The smooth and high-yield reaction of TMSCl affording **4b**, **6b**, and **9b** is indoubtedly related to its *in situ* compatibility with LTMP at low temperature.[51] Whereas MeI quenches at −50 °C left **2** unreacted, *in situ* trapping with TMSCl at −78 °C provided 2-trimethylsilyl-3-methoxybenzoic acid (**6b**)

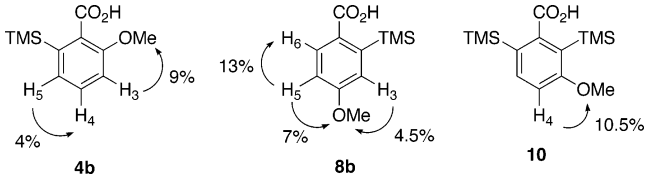
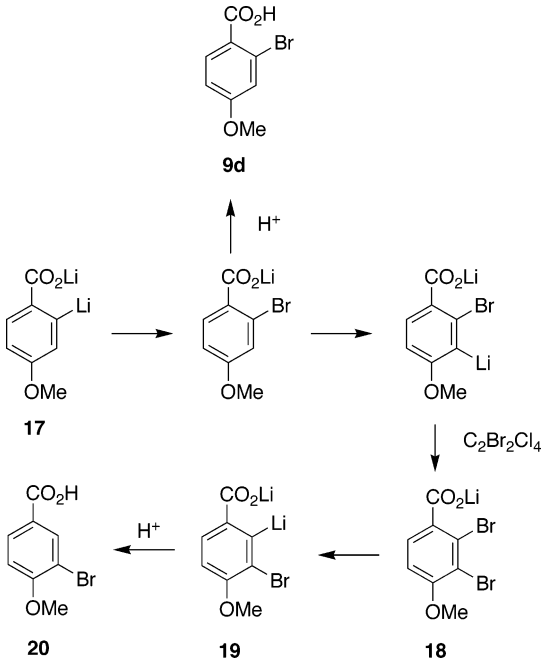


FIGURE 3. Determination of the location of the TMS group of **4b**, **8b**, and **10** by qualitative homonuclear NOE difference spectroscopy.

SCHEME 2



in 75% yield. In another chromatographic fraction, 3-methoxy-2,6-bis(trimethylsilyl)benzoic acid (**10**) resulting from the partial deprotonation of lithium salt of the primary product **6b** by the excess of base at the carbon C-6 was also isolated. Bissilylation was cleanly achieved if LTMP was used in large excess (5 equiv) at 0 °C under ISQ conditions (51%).

Proof for the location of the TMS group of **4b**, **8b**, and **10** is gathered by qualitative homonuclear NOE difference spectroscopy **(**Figure 3). Individual irradiations of H_3 (H_5) for **4b** show an enhancement of the neighboring OMe (9%) (H_4 (4%), respectively). For **8b**, irradiation of H_3 results in an enhancement of the methoxy group (4.5%) while irradiation of H_5 causes large enhancement of two signals, namely OMe (7%) and H_6 (13%). Irradiation of H_4 for **10** results in a 10.5% NOE of the methoxy group.

A variety of chlorine, bromine, and iodine derivatives were conveniently obtained from reactions with hexachloroethane, 1,2-dibromotetrachloroethane, and iodine as electrophiles. Reaction of *p*-anisic (**3**) with $C_2Br_2Cl_4$ led to a mixture of **9d** and **20** (54%, 48:52, Scheme 2). The lithium (2-carboxylato-5-methoxyphenyl)lithium component (**17**) is partly converted into the thermodynamically more stable lithium (2-bromo-6-carboxylato-3-methoxyphenyl)lithium (**19**), lithium 2,3-dibromo-4-methoxybenzoate (**18**) acting as the presumed turntable for this new example of a halogen migration ("dance").[52] The latter

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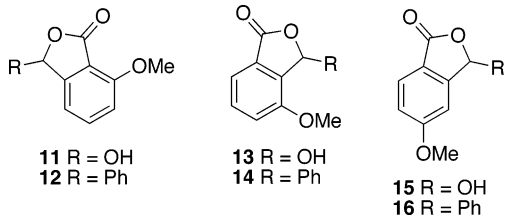

FIGURE 4. Hydroxyphthalides and lactones **11**−**16**.

isomerization can be readily explained if reversibility of the lithiation is assumed.

Addition of dimethyl disulfide afforded the methylsulfenylated derivatives **4**−**6f**, **7e**, and **8e**. In cases where DoM occurs at the position adjacent to the carboxylate group (routes A, C, and F), the primary products obtained with DMF (**4**, **6**, **9g**) and benzaldehyde (**4**, **6**, **9h**) after acidic hydrolysis were directly transformed into hydroxyphthalides and lactones **11**−**16** (Figure 4).[53] Hydroxyphthalides are intermediates for assembly of anthracyclinone-type antibiotics.[54]

Of special interest is the ability of the carboxylate to introduce an allyl substituent. Reaction of *N*,*N*-diisopropylbenzamide or 2-methoxy-*N*,*N*-diethylbenzamide with allyl bromide under standard conditions (*s*-BuLi−TMEDA complex, −78 °C, THF) provided the bromides instead of the allylated derivatives.[12] Allylation of tertiary benzamides can only be achieved by prior transformation of the aryllithium to the corresponding softer ortho cuprate reagents.[1a] Nevertheless, it should be noted that significant amounts of byproducts are frequently formed in these condensations, probably due to the thermal instability of the lithio-cuprate species.[55] The one-pot lithiation/oxygenation sequence (LTMP; then O_2) afforded a moderate yield of regiospecifically monohydroxylated product **6i**.[56]

Conclusion

A systematic study has provided conditions for selective ortho metalation of anisic acids. Synthetic utility has been demonstrated by the provision of functionalized derivatives **4**−**9**. The use of the carboxylate group as ortho-metalation directing groups has several notable advantages over that of the corresponding secondary or tertiary benzamides. The synthetic potential thereof would appear to match if not exceed that of tertiary benzamides as ortho-lithiation directing groups. A discussion of the subtle effects of base aggregates, complexing abilities of the substituents, and base strengths must await further studies, but it is clear that predicting sites of metalation in multiply substituted aromatics is difficult and should be approached with caution. In view of the number of groups that promote aromatic directed metalation,[1] the results reported herein may have broader synthetic implications for polysubstituted aromatic and heteroatom ring annelation methodologies.

(53) Under conditions B, the reaction leads to degradation products with DMF, allyl bromide, and benzyl bromide. Acid **2** also leads to degradation products by reaction with DMF under conditions D.

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Experimental Section

For standard working practice, see ref 57. Reactions were carried out under argon in oven-dried glassware. Tetrahydrofuran was dried from sodium benzophenone. Iodomethane, *N*,*N*-dimethylformamide, and benzaldehyde were dried with CaH_2 and distilled prior to use. NMR spectra were recorded on a 200- or 400-MHz spectrometer. ^{13}C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, chemical shifts were recorded relative to the internal TMS (tetramethylsilane) reference signal. For DMSO-d_6, chemical shifts are given relative to the solvent signals. All melting points are uncorrected. *n*-BuLi (1.6 M in hexanes) and *s*-BuLi (1.3 M in cyclohexane−hexanes) were titrated periodically against 2,5-dimethoxybenzyl alcohol. *N*,*N*,*N*′,*N*′-Tetramethyl-1,2-ethylenediamine (TMEDA) was distilled from CaH_2. Potassium *tert*-butylate (*t*-BuOK) was sublimated.

General Procedure for the Preparation of 6-Substituted 2-Methoxybenzoic Acids (4a-f,i,j). Preparation of 3-Hydroxy-7-methoxyisobenzofuran-1(3*H*)-one (11) and 7-Methoxy-3-phenylisobenzofuran-1(3*H*)-one (12) (route A). To a stirred solution of a 1:1 *s*-BuLi/TMEDA complex (11 mmol) in anhydrous THF at −78 °C was added dropwise under argon *o*-anisic acid (**1**) (0.76 g, 5 mmol) dissolved in dry THF (5 mL). After 2 h at this temperature, the mixture was treated with an excess of the appropriate electrophile (20 mmol) dissolved in THF. The resulting solution was then slowly allowed to warm to ambient temperature, and water was added. The aqueous layer was washed with diethyl ether (2 × 30 mL), shaken, and acidified with 2 M HCl. The mixture was then diluted with diethyl ether, and the organic layer was separated and dried with $MgSO_4$.

2-Methoxy-6-methylbenzoic Acid (4a). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by MeI (2.84 g, 20 mmol). Workup in the usual manner followed by recrystallization (heptane/ethyl acetate) afforded **4a** (0.51 g, 61%) as a white solid: mp 138.5−139.0 °C (lit.[4] 137−138 °C). ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 2.45 (s, 3H), 3.88 (s, 3H), 6.82 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 7.29 (t, 1H, $J = J$ = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.6, 56.6, 109.2, 122.1, 123.6, 131.6, 138.7, 157.4, 173.1. IR (neat): 2995, 1692, 1585, 1471, 1267, 1087, 915 cm^{-1}. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.03; H, 6.05.

2-Methoxy-6-(trimethylsilyl)benzoic Acid (4b) (*in situ* quench technique). To a solution of LTMP (9 mmol) in THF (20 mL) at −78 °C were added successively TMSCl (1.38 mL, 10.5 mmol) in THF (5 mL) and *o*-anisic acid (**1**) (0.46 g, 3 mmol) in THF (3 mL). After being warmed gradually to rt for 4 h, aqueous 2 M NaOH was added until the pH reached 10. The aqueous layer was washed with diethyl ether, acidified with aqueous 4 M HCl, and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by colum chromatography on silica gel (cyclohexane/diethyl ether 90:10) to give **4b** (0.60 g, 89%) as a white solid (mp 85.5−87.0 °C). ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.33 (s, 9H), 3.98 (s, 3H), 7.05 (d, 1H, J = 8.4 Hz), 7.37 (d, 1H, J = 7.8 Hz), 7.51 (dd, 1H, J = 8.4 Hz, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 0.6 (3C), 56.0, 112.1, 124.2, 127.9, 131.8, 144.4, 157.2, 170.3. IR (neat): 2840, 1681, 1571, 1445, 1243, 1126, 950 cm^{-1}. Anal. calcd. for $C_{11}H_{16}O_3Si$: C, 58.89; H, 7.19. Found: C, 58.94; H, 7.12.

2-Chloro-6-methoxybenzoic Acid (4c). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by hexachloroethane (4.73 g, 20 mmol). Workup in the usual manner followed by chroma-

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tography (cyclohexane/ethyl acetate 80:20) afforded **4c** (0.54 g, 58%) as a white solid: mp 142.5−144 °C (lit.[26] 140−141 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.88 (s, 3H), 6.88 (dd, 1H, J = 8.4 Hz, J = 0.8 Hz), 7.03 (dd, 1H, J = 8.2 Hz, J = 0.8 Hz), 7.29 (dd, 1H, J = 8.4 Hz, J = 8.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 56.1, 110.4, 120.9, 124.9, 129.2, 130.9, 156.3, 165.9. IR (neat): 2839, 2531, 1713, 1589, 1467, 1262, 1029, 924 cm^{-1}. Anal. Calcd for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found: C, 51.81; H, 3.71.

2-Bromo-6-methoxybenzoic Acid (4d). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by dibromotetrachloroethane (6.51 g, 20 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 80:20) afforded **4d** (0.68 g, 59%) as a white solid: mp 127−129 °C (lit.[22g] 124−127 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.89 (s, 3H), 6.87 (dd, 1H, J = 8.4 Hz, J = 0.8 Hz), 7.02 (dd, 1H, J = 8.1 Hz, J = 0.8 Hz), 7.32 (dd, 1H, J = 8.4 Hz, J = 8.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 56.3, 109.6, 121.7, 122.7, 131.5, 131.6, 157.3, 171.3. IR (neat): 2841, 1719, 1589, 1469, 1262 cm^{-1}.

2-Iodo-6-methoxybenzoic Acid (4e). According to the general procedure, the recrystallized *o*-anisic (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by iodine (5.07 g, 20 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 80:20) afforded **4e** (0.64 g, 46%) as a brown solid: mp 129−131 °C (lit.[27] 128−130 °C). ^{1}H NMR (200 MHz, $CDCl_3$) 3.84 (s, 3H), 6.92 (dd, 1H, J = 8.4 Hz, J = 0.9 Hz), 7.10 (dd, 1H, J = 8.4 Hz, J = 8.1 Hz), 7.44 (dd, 1H, J = 8.1 Hz, J = 0.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 56.6, 92.2, 110.9, 129.2, 131.2, 131.9, 156.7, 172.6. IR (neat): 2841, 1719, 1589, 1469, 1262 cm^{-1}.

2-Methoxy-6-(methylthio)benzoic Acid (4f). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by dimethyl disulfide (1.88 g, 20 mmol). Workup in the usual manner followed by recrystallization (cyclohexane/ethyl acetate) afforded **4f** (0.47 g, 47%) as a white solid: mp 182−184 °C (lit.[28] 184−185 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 2.45 (s, 3H), 3.98 (s, 3H), 6.80 (d, 1H, J = 8.2 Hz), 6.98 (d, 1H, J = 8.2 Hz), 7.40 (t, 1H, J = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 17.0, 56.6, 107.6, 107.9, 119.4, 131.9, 142.6, 157.9, 169.1. IR (neat): 2941, 1688, 1578, 1461, 1261, 1040, 927 cm^{-1}. Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.41; H, 5.01.

3-Hydroxy-7-methoxyisobenzofuran-1(3*H*)-one (11). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by DMF (1.46 g, 20 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 70:30) afforded **11** (0.39 g, 43%) as a white solid: mp 155−157 °C (lit.[29] 155−156 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.99 (s, 3H), 6.53 (s, 1H), 7.01 (d, 1H, J = 8.4 Hz), 7.18 (d, 1H J = 7.4 Hz), 7.53 (dd, 1H, J = 8.4 Hz, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 55.6, 96.5, 112.3, 115.1, 121.2, 130.6, 133.0, 158.0, 167.3. IR (neat): 2987, 1754, 1601, 1486, 1296, 1197, 1027 cm^{-1}.

7-Methoxy-3-phenylisobenzofuran-1(3*H*)-one (12). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by benzaldehyde (2.12 g, 20 mmol). Workup in the usual manner followed by recrystallization (cyclohexane/ethyl acetate 70:30) afforded **12** (0.624 g, 52%) as a white solid: mp 136−138 °C (lit.[30] 139−141.5 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 4.02 (s, 3H), 6.31 (s, 1H), 6.84 (d, 1H, J = 7.6 Hz), 6.94 (d, 1H, J = 8.4 Hz), 7.25−7.39 (m, 5H), 7.53 (dd, 1H, J = 7.6 Hz, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 56.1, 81.6, 110.9, 112.9, 114.5, 126.9, 128.9 (2C), 129.1 (2C), 136.6, 136.7, 152.5, 158.5, 168.6. IR (neat): 2985, 1754, 1600, 1486, 1296, 1196, 1027 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.56; H, 5.03.

2-Allyl-6-methoxybenzoic Acid (4i). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by allyl bromide (2.42 g, 20 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 85:15) afforded **4i** (0.43 g, 45%) as a white solid: mp 89−91 °C (lit.[31] 91 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.54 (d, 2H, J = 6.7 Hz), 3.89 (s, 3H), 5.04−5.15 (m, 2H), 5.97 (m, 1H), 6.85 (d, 1H, J = 8.2 Hz), 6.91 (d, 1H, J = 7.8 Hz), 7.34 (dd, 1H, J = 8.2 Hz, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 37.9, 56.1, 109.3, 116.4, 122.1, 122.3, 131.2, 136.4, 139.6, 156.8, 172.9. IR (neat): 2951, 1685, 1581, 1471, 1289, 1061, 918 cm^{-1}.

2-Benzyl-6-methoxybenzoic Acid (4j). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by benzyl bromide (3.40 g, 20 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 80:20) afforded **4j** (0.57 g, 47%) as a white solid: mp 148−149.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.90 (s, 3H), 4.14 (s, 2H), 6.82 (dd, 2H, J = 7.9 Hz, J = 9.9 Hz), 7.16−7.34 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 39.2, 56.1, 108.9, 109.2, 122.8, 126.3, 128.4 (2C), 129.2 (2C), 131.2, 140.0, 140.8, 156.8, 172.6. IR (neat): 2941, 1690, 1597, 1469, 1293, 1080, 932 cm^{-1}.

General Procedure for the Preparation of 3-Substituted 2-Methoxybenzoic Acids (5a−g) (route B). *o*-Anisic acid (**1**) (0.46 g, 3 mmol) in THF (5 mL) was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol) in THF (30 mL) at −78 °C. After being stirred at −78 °C for 2 h, the reaction mixture was quenched with the electrophile (18 mmol) in THF (5 mL). Stirring was maintained for 1 h, and the resulting mixture was allowed to warm to rt and hydrolyzed with water (30 mL). The aqueous layer was washed with diethyl ether (2 × 30 mL), acidified with aqueous (2 M) HCl until pH reached 1, and extracted with diethyl ether (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude benzoic acids (**5a**−**g**) which were purified by chromatography or fractional crystallization.

2-Methoxy-3-methylbenzoic Acid (5a). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol). The solution was quenched by MeI (2.55 g, 18 mmol). Workup in the usual manner followed by recrystallization (cyclohexane/ethyl acetate) afforded **5a** (0.199 g, 40%) as a white solid: mp 81−83 °C (lit.[32] 83−83.5). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 2.37 (s, 3H), 3.93 (s, 3H), 7.17 (dd, 1H J = 7.8 Hz, J = 7.4 Hz), 7.43 (d, 1H, J = 7.4 Hz), 7.91 (d, 1H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 16.0, 62.1, 122.2, 124.8, 130.6, 131.9, 136.9, 158.1, 167.6. IR (neat): 2833, 2575, 1667, 1589, 1468, 1307, 1089, 949 cm^{-1}. HRMS (EI) m/z calcd. for $C_9H_{10}O_3$ ($M^{+\bullet}$): 166.0629. Found: 166.0628.

2-Methoxy-3-(trimethylsilyl)benzoic Acid (5b). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol). The solution was quenched by TMSCl (1.96 g, 18 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 90:10) afforded **5b** (0.269 g, 40%) as a white solid: mp 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.34 (s, 9H), 3.89 (s, 3H), 7.21 (t, 1H, J = 7.3 Hz), 7.64 (dd, 1H, J = 7.3 Hz, J = 1.8 Hz), 8.04 (dd, J = 7.6 Hz, J = 1.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 0.6 (3C), 63.7, 121.6, 124.2, 134.5, 135.0, 141.2, 166.1, 170.6. IR (neat): 2947, 2651, 1677, 1579, 1452, 1298, 1127, 920 cm^{-1}. HRMS (EI) m/z calcd. for $C_{11}H_{16}O_3Si$ ($M^{+\bullet}$): 224.0868. Found: 224.0860.

3-Chloro-2-methoxybenzoic Acid (5c). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.46 g, 3 mmol) in

THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol). The solution was quenched by hexachloroethane (4.26 g, 18 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 80:20) afforded **5c** (0.218 g, 39%) as a yellow solid: mp 114−116 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 4.06 (s, 3H), 7.21 (t, 1H, J = 8.0 Hz), 7.62 (dd, 1H, J = 8.0 Hz, J = 1.6 Hz), 7.99 (dd, 1H, J = 8.0 Hz, J = 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 62.5, 124.6, 125.3, 129.0, 131.2, 135.7, 155.9, 167.6. IR (neat): 2826, 2558, 1667, 1586, 1463, 1234, 1076, 917 cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_8H_7O_3Cl$ ($M^{+\bullet}$): 186.0083. Found: 186.0079.

3-Bromo-2-methoxybenzoic Acid (5d). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol). The solution was quenched by dibromotetrachloroethane (5.86 g, 18 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 80:20) afforded **5d** (0.235 g, 34%) as a white solid: mp 119−121 °C (lit.[33] 121 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 4.07 (s, 3H), 7.22 (t, 1H, J = 8.0 Hz), 7.63 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz), 8.01 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 61.6, 124.9, 125.1, 128.2, 129.5, 133.4, 154.5, 166.4. IR (neat): 2952, 1669, 1588, 1465, 1222, 1077, 992 cm^{-1}.

3-Iodo-2-methoxybenzoic Acid (5e). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol). The solution was quenched by iodine (4.57 g, 18 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 80:20) afforded **5e** (0.225 g, 27%) as a white solid: mp 122−124 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.99 (s, 3H), 7.01 (t, 1H, J = 7.8 Hz), 8.00−8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 62.8, 93.1, 123.9, 126.4, 132.3, 144.9, 159.6, 168.1. IR (neat): 2924, 1673, 1581, 1456, 1402, 1296, 1074, 992 cm^{-1}.

2-Methoxy-3-(methylthio)benzoic Acid (5f). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol). The solution was quenched by dimethyl disulfide (1.69 g, 18 mmol). Workup in the usual manner followed by recrystallization (cyclohexane/ethyl acetate) afforded **5f** (0.27 g, 45%) as a white solid: mp 77−79 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 2.49 (s, 3H), 4.03 (s, 3H), 7.25 (t, 1H, J = 7.8 Hz), 7.42 (dd, 1H, J = 7.8 Hz, J = 1.6 Hz), 7.89 (dd, 1H, J = 7.8 Hz, J = 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.8, 61.7, 124.5, 124.9, 128.3, 130.1, 134.2, 156.1, 168.5. HRMS (EI) *m*/*z* calcd. for $C_9H_{10}O_3S$ ($M^{+\bullet}$): 198.0350. Found: 198.0339.

3-(Hydroxy(phenyl)methyl)-2-methoxybenzoic Acid (5g). According to the general procedure, the recrystallized *o*-anisic acid (**1**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 mmol). The solution was quenched by benzaldehyde (1.91 g, 18 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethyl acetate 70:30) afforded **5g** (0.318 g, 41%) as a white solid: mp 124−126 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.72 (s, 3H), 6.16 (s, 1H), 7.23−7.30 (m, 3H), 7.31−7.38 (m, 3H), 7.69 (dd, 1H, J = 7.6 Hz, J = 1.5 Hz), 7.98 (dd, 1H, J = 7.8 Hz, J = 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 63.1, 71.0, 124.4, 126.6, 127.7, 128.5, 132.2, 133.4, 138.3, 143.1, 158.0, 171.5. IR (neat): 3427, 2939, 1708, 1590, 1429, 1210, 992, 752 cm^{-1}.

General Procedure for the Preparation of 2-Substituted 3-Methoxybenzoic Acids (6a-f). Preparation of 3-Hydroxy-4-methoxyisobenzofuran-1(3*H*)-one (13) and 4-Methoxy-3-phenylisobenzofuran-1(3*H*)-one (14) (route C). To a stirred solution of LTMP (5 equiv) in THF (20 mL) at 0 °C was added dropwise *m*-anisic (**2**) (0.46 g, 3 mmol) in THF (5 mL). After being stirred 2 h at this temperature, the solution was quenched with the electrophile (6−10 equiv). Stirring was maintained for 30 min, and the solution was then allowed to warm to ambient temperature or heated to 40−65 °C for 2 h. After hydrolysis with water (30 mL), the aqueous phase was washed with diethyl ether (20 mL), acidified with aqueous (2 M) HCl, and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude benzoic acids which were chromatographed on silica gel or recrystallized.

3-Methoxy-2-methylbenzoic Acid (6a). See general procedure. The solution was quenched with iodomethane (1.9 mL, 30 mmol). After being stirred for 30 min at 0 °C, the reaction mixture was heated for 2 h at 40 °C. Standard workup followed by chromatography (cyclohexane/ethyl acetate 80:20, R_f = 0.29) afforded **6a** (0.25 g, 50%) as a white solid (mp 145−146 °C, lit.[34] 146.5−149.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 3.87 (s, 3H), 7.04 (d, 1H, J = 8.4 Hz), 7.20−7.26 (dd, 1H, J = 8.4 Hz and J = 7.8 Hz), 7.61 (d, 1H, J = 7.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.3, 56.3, 114.7, 123.3, 126.5, 130.2, 130.6, 158.5, 174.3. IR (neat): 2646, 1682, 1583 cm^{-1}. Anal. calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.01; H, 6.01.

3-Methoxy-2-(trimethylsilyl)benzoic Acid (6b) (in situ quench technique). To a solution of LTMP (9 mmol) in THF (20 mL) at −78 °C were added successively TMSCl (1.38 mL, 10.5 mmol) in THF (5 mL) and *m*-anisic acid (**2**) (0.46 g, 3 mmol) in THF (5 mL). After being warmed gradually to 0 °C for 2 h, the solution was allowed to warm to ambient temperature. Aqueous (2 M) NaOH was added until the pH reached 10. The aqueous layer was washed with diethyl ether, acidified with aqueous (4 M) HCl, and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by colum chromatography on silica gel (cyclohexane/ethyl acetate 90:10, R_f = 0.31) to give **6b** (0.51 g, 75%) as a white solid (mp 91−92 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.33 (s, 9H), 3.82 (s, 3H), 7.01 (d, 1H, J = 7.8 Hz), 7.35−7.64 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 0.6, 54.1, 112.1, 120.1, 126.9, 129.0, 137.9, 163.7, 175.1. IR (neat): 2959, 2560, 1673 cm^{-1}. Anal. calcd. for $C_{11}H_{16}O_3Si$: C, 58.89; H, 7.19. Found: C, 58.91; H, 7.17.

3-Methoxy-2,6-bis(trimethylsilyl)benzoic Acid (10). To a stirred solution of LTMP (15 mmol) in THF (20 mL) at 0 °C were added successively **2** (0.46 g, 3 mmol) in THF (5 mL) and chlorotrimethylsilane (1.38 mL, 10.5 mmol). After being stirred for 2 h at 0 °C, the solution was allowed to warm to ambient temperature. Aqueous (2 M) NaOH was added up to pH 10, and the aqueous layer was washed with diethyl ether, acidified with aqueous (4M) HCl, and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude acid **10** was purified by chromatography (cyclohexane/ethyl acetate 90:10, R_f = 0.29) to give a yellow solid (0.45 g, 51%) (mp 142−144 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.31 (s, 9H), 0.33 (s, 9H), 3.82 (s, 3H), 6.91 (d, 1H, J = 8.4 Hz), 7.58 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.5, 1.3, 55.2, 111.0, 126.1, 128.8, 137.7, 145.1, 165.3, 178.0. IR (neat): 2940, 1679 cm^{-1}.

2-Chloro-3-methoxybenzoic Acid (6c). See general procedure. The solution was quenched with hexachloroethane (4.27 g, 18 mmol). After being stirred for 30 min at 0 °C, the mixture was heated at 65 °C for 2 h. Standard workup followed by chromatography (cyclohexane/ethyl acetate 80:20, R_f = 0.13) gave **6c** (0.263 g, 47%) as a white solid (mp 160−161 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.95 (s, 3H), 7.13 (dd, 1H, J = 8.4 Hz and J = 1.5 Hz), 7.32 (dd, 1H, J = 7.9 Hz and J = 8.4 Hz), 7.56 (dd, 1H, J = 7.9 Hz and J = 1.5 Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 56.4, 114.6, 119.3, 121.2, 127.7, 133.8, 150.0, 167.1. IR (neat): 2938, 1679, 1574 cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_8H_7O_3Cl$ ($M^{+\bullet}$): 186.0083. Found: 186.0076.

2-Bromo-3-methoxybenzoic Acid (6d). See general procedure. The solution was quenched with dibromotetrachloroethane (5.87 g 18 mmol). After being stirred for 30 min at 0 °C, the solution was heated at 65 °C for 2 h. Standard workup followed by chromatography (cyclohexane/ethyl acetate 80:20, R_f = 0.15) afforded **6d** (0.414 g, 60%) as a brown solid (mp 154−155 °C, lit.[35] 155−156 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.98 (s, 3H), 7.07 (dd,

1H, $J = 7.8$ Hz and $J = 1.5$ Hz), 7.38 (t, 1H, $J = 7.8$ Hz), 7.52 (dd, 1H, $J = 7.8$ Hz and $J = 1.5$ Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 56.7, 109.1, 114.4, 121.4, 129.0, 137.0, 156.1, 168.3. IR (neat): 2941, 1680, 1570 cm^{-1}. Anal. calcd. for $C_8H_7BrO_3$: C, 41.59; H, 3.05. Found: C, 41.56; H, 3.11. HRMS (EI) *m*/*z* calcd. for $C_8H_7O_3{}^{79}Br$ ($M^{+\bullet}$): 229.9578. Found: 229.9577.

2-Iodo-3-methoxybenzoic Acid (6e). See general procedure. The solution was quenched with iodine (4.57 g, 18 mmol). After being stirred for 30 min at 0 °C, the mixture was heated at 65 °C for 2 h. Standard workup followed by chromatography (cyclohexane/ethyl acetate 80:20) gave **6e** (0.442 g, 53%) as a yellow solid (mp 145−146 °C, lit.[36] 148−149 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94 (s, 3H), 6.99 (dd, 1H, $J = 7.9$ Hz and $J = 1.5$ Hz), 7.38 (t, 1H, $J = 7.9$ Hz), 7.49 (dd, 1H, $J = 7.9$ Hz and $J = 1.5$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 56.9, 87.5, 114.1, 123.6, 129.3, 136.7, 158.9, 172.5. IR (neat): 2927, 1738, 1609 cm^{-1}. HRMS (EI) *m*/*z* calcd.for $C_8H_7O_3I$ ($M^{+\bullet}$): 277.9440. Found: 277.9445.

3-Methoxy-2-methylthiobenzoic Acid (6f). See general procedure. The solution was quenched with dimethyl disulfide (1.6 mL, 18 mmol). Standard workup followed by chromatography (cyclohexane/ethyl acetate 60:40, $R_f = 0.39$) afforded **6f** (0.273 g, 46%) as a brown-red solid (mp 132−134 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 3.96 (s, 3H), 7.09 (dd, 1H, $J = 8.4$ Hz), 7.40 (dd, 1H, $J = 8.4$ Hz and $J = 7.9$ Hz), 7.65 (dd, 1H, $J = 7.9$ Hz and $J = 1.0$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.2, 56.7, 114.7, 122.9, 123.9, 129.8, 136.3, 160.5, 171.8. IR (neat): 2926, 1739, 1609 cm^{-1}. Anal. calcd. for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.28; H, 5.13.

3-Hydroxy-4-methoxyisobenzofuran-1(3*H*)-one (13). See general procedure. The solution was quenched with *N*,*N*-dimethylformamide (1.4 mL, 18 mmol). Usual workup followed by chromatography (cyclohexane/ethyl acetate 60:40, $R_f = 0.24$) afforded **13** (0.146 g, 27%) as a white solid (mp 154−155 °C, lit.[37] 156−157 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3,96 (s, 3H), 6.70 (s, 1H), 7.17 (d, 1H, $J = 7.9$ Hz), 7.47 (d, 1H, $J = 6.9$ Hz), 7.57 (dd, 1H, $J = 7.9$ Hz, $J = 6.9$ Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 56.2, 97.5, 116.4, 117.3, 128.7, 133.0, 134.5, 155.5, 168,8.

4-Methoxy-3-phenylisobenzofuran-1(3*H*)-one (14). See general procedure. The solution was quenched with benzaldehyde (1.84 mL, 18 mmol). Standard workup followed by chromatography (cyclohexane/ethyl acetate 60:40, $R_f = 0.59$) afforded **14** (0.468 g, 65%) as a white solid (mp 147−148 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 6.40 (s, 1H), 7.08 (dd, 1H, $J = 7.5$ Hz and $J = 1.5$ Hz), 7.25−7.28 (m, 1H), 7.33−7.35 (m, 1H), 7.5−7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 81.7, 115.6, 117.1, 127.1, 128.8, 129.0, 131.4, 135.7, 137.2, 154.6, 170.5. IR (neat): 2926, 1739, 1609 cm^{-1}. Anal. calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.56; H, 5.05.

2-Hydroxy-3-methoxybenzoic Acid (6i). See general procedure. O_2 was bubbled through the rapidly stirring solution.[56] Standard workup followed by chromatography (cyclohexane/ethyl acetate 80:20) afforded **6i** (0.272 g, 54%) as a white solid (mp 150−152 °C, lit.[38] 151 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 6.89 (d, 1H, $J = 7.9$ Hz), 7.11 (d, 1H, $J = 7.9$ Hz), 7.54 (t, 1H, $J = 7.9$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 56.3, 111.8, 117.5, 118.9, 122.0, 148.5, 152.5, 174.5. IR (neat): 3018, 2866, 1618, 1455, 1254 cm^{-1}.

General Procedure for the Preparation of 4-Substituted 3-Methoxybenzoic Acids (7a-f) (route C). *m*-Anisic acid (**2**, 0.46 g, 3 mmol) in THF (5 mL) was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1, 12 equiv) in THF (30 mL) at −78 °C. After being stirred for 2 h (−78 °C → −50 °C), the reaction mixture was quenched with the electrophile (18 mmol). Stirring was maintained for 30 min at −50 °C, and the resulting mixture was allowed to warm to rt and hydrolyzed with water (30 mL). The aqueous layer was washed with diethyl ether (20 mL), acidified with aqueous (2 M) HCl, and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude benzoic acids (**7a**−**f**) which were purified by chromatography or fractional crystallization.

3-Methoxy-4-methylbenzoic Acid (7a). See general procedure. The solution was quenched with iodomethane (1.12 mL, 18 mmol). Standard workup followed by fractional crystallization (cyclohexane/ethyl acetate) led to **7a** (0.294 g, 59%) as a white solid (mp 210−213 °C, lit.[21b] 212−214 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 3.89 (s, 3H), 7.18 (d, 1H, $J = 7.8$ Hz), 7.58 (s, 1H), 7.74 (d, 1H, $J = 7.8$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.5, 55.6, 110.7, 121.9, 130.0, 130.1, 130.7, 157.4, 167.6. IR (neat): 2960, 1673, 1609 cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_9H_{10}O_3$ ($M^{+\bullet}$): 166.0630. Found: 166.0631.

4-Chloro-3-methoxybenzoic Acid (7b). See general procedure. The solution was quenched with hexachloroethane (4.26 g, 18 mmol). Standard workup followed by fractional crystallization (cyclohexane/ethyl acetate) led to **7b** (0.217 g, 39%) as a brown solid (mp 210−212 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.98 (s, 3H), 7.48 (d, 1H, $J = 7.8$ Hz), 7.62 (s, 1H), 7.69 (dd, 1H, $J = 7.8$ Hz and $J = 1.5$ Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 56.1, 112.7, 122.3, 125.9, 129.9, 130.9, 154.4, 166.5. IR (neat): 2975, 1678 cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_8H_7ClO_3$ ($M^{+\bullet}$): 186.00837. Found: 186.0079.

4-Bromo-3-methoxybenzoic Acid (7c). See general procedure. The solution was quenched with dibromotetrachloroethane (5.87 g, 18 mmol,). Standard workup followed by fractional crystallization (cyclohexane/ethyl acetate) afforded **7c** (0.312 g, 45%) as a white solid (mp 212−213 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.99 (s, 3H), 7.64 (s, 1H), 7.67−7.68 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 56.1, 112.5, 116.0, 122.3, 130.9, 132.1, 155.4, 166.6. IR (neat): 2970, 1679 cm^{-1}.

4-Iodo-3-methoxybenzoic Acid (7d). See general procedure. The solution was quenched with iodine (4.57 g, 18 mmol). Standard workup followed by fractional crystallization (cyclohexane/ethyl acetate) afforded **7d** (0.167 g, 20%) as a white solid (mp 210−212 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.04 (s, 3H), 7.45 (dd, 1H, $J = 8.4$ Hz and $J = 1.5$ Hz), 7.57 (d, 1H, $J = 1.5$ Hz), 8.06 (d, 1H, $J = 8.4$ Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 56.4, 92.6, 111.2, 123.2, 132.5, 139.3, 157.9, 166.8. IR (neat): 2960, 1673, 1608 cm^{-1}.

3-Methoxy-4-thiomethylbenzoic Acid (7e). See general procedure. The solution was quenched with dimethyldisulfide (18 mmol, 1.6 mL). Standard workup followed by fractional crystallization (cyclohexane/ethyl acetate) afforded **7e** (0.303 g, 51%) as a yellow solid (mp 186−187 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H), 3.97 (s, 3H), 7.16 (d, 1H, $J = 8.4$ Hz), 7.51 (d, 1H, $J = 1.5$ Hz), 7.75 (dd, 1H, $J = 8.4$ Hz and $J = 1.5$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.2, 56.7, 114.7, 122.9, 123.9, 129.8, 136.3, 160.5, 171.8. IR (neat): 2970, 1674, 1592 cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_9H_{10}O_3S$ ($M^{+\bullet}$): 198.0351. Found: 198.0361.

4-(Hydroxy(phenyl)methyl)-3-methoxybenzoic Acid (7f). See general procedure. The solution was quenched with benzaldehyde (18 mmol, 1.84 mL). Standard workup followed by chromatography (cyclohexane/ethyl acetate 60:40, $R_f = 0.28$) gave **7f** (0.389 g, 54%) as a yellow solid (mp 122−124 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 6.11 (s, 1H), 7.27−7.42 (m, 5H), 7.47 (d, 1H, $J = 7.8$ Hz). 7.58 (d, 1H, $J = 1.6$ Hz), 7.75 (dd, 1H, $J = 7.8$ Hz and $J = 1.6$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 26.3, 55.5, 67.9, 110.9, 121.9, 126.4, 126.7, 128.0, 130.3, 138.6, 144.6, 155.3, 167.1. IR (neat): 3342, 2927, 1677 cm^{-1}.

General Procedure for the Preparation of 6-Substitued 3-Methoxybenzoic Acids (8a-e) (route E). To a stirred solution of *s*-BuLi/TMEDA (4 mmol) in dry THF (5 mL) at −78 °C was added dropwise 3-methoxy-2-(trimethylsilyl)benzoic acid (**6b**) (0.224 g, 1 mmol) in dry THF (5 mL). After being stirred for 2 h (−78 °C → −30 °C), the reaction mixture was quenched with the electrophile (6 mmol). Stirring was maintained for 30 min at −30 °C, and the resulting mixture was allowed to warm to rt and hydrolyzed with water (20 mL). The aqueous layer was washed with diethyl ether (2 × 20 mL), acidified with aqueous (2 M) HCl

until the pH reached 2, and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was hydrolyzed with aqueous (6 M) HCl to pH 1 to give the crude 6-substitued 3-methoxybenzoic acids (**8a**−**e**) which were purified by column chromatography or recrystallization.

6-Methyl-3-methoxybenzoic Acid (8a). See general procedure. After purification by recrystallization (*n*-heptane/ethyl acetate), the acid **8a** was obtained as a white solid (0.090 g, 54%) (mp 151−152 °C, lit.[39] 151−151.5 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.59 (s, 3H), 3.83 (s, 3H), 7.02 (dd, 1H, J = 8.4 Hz and J = 2.9 Hz), 7.16 (d, 1H, J = 8.4 Hz), 7.58 (d, 1H, J = 2.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.6, 55.6, 115.2, 117.9, 121.9, 131.0, 132.7, 157.4, 168.9. HRMS (EI) *m*/*z* calcd. for $C_9H_{10}O_3$ ($M^{+\bullet}$): 166.0630. Found: 166.0628.

6-Chloro-3-methoxybenzoic Acid (8b). See general procedure. After recrystallization (cyclohexane/ethyl acetate), the acid **8b** was obtained as a colorless solid (0.102 g, 55%) (mp 168−169.5 °C, lit.[40] 169−171 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 7.02 (dd, 1H, J = 8.8 Hz and J = 3.1 Hz), 7.38 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 3.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.6, 115.5, 118.3, 122.6, 131.4, 132.2, 157.7, 166.5. IR (neat): 2945, 1672 cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_8H_7O_3Cl$ ($M^{+\bullet}$): 186.0084. Found: 186.0094.

6-Bromo-3-methoxybenzoic Acid (8c). See general procedure. After chromatography (cyclohexane/ethyl acetate 80:20, R_f = 0.15), the acid **8c** was obtained as a colorless solid (0.145 g, 63%) (mp 158−160 °C, lit.[41] 160 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 6.95 (dd, 1H, J = 8.8 Hz and J = 3.1 Hz), 7.54 (d, 1H, J = 3.1 Hz), 7.59 (d, 1H, J = 8.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.7, 112.9, 117.1, 120.6, 130.9, 135.6, 158.6, 170.9.

6-Iodo-3-methoxybenzoic Acid (8d). See general procedure. After chromatography (cyclohexane/ethyl acetate 80:20, R_f = 0.16), the acid **8d** was obtained as a white solid (0.139 g, 50%) (mp 132.5−134 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 6.81 (dd, 1H, J = 8.8 Hz and J = 3.1 Hz), 7.57 (d, 1H, J = 3.1 Hz), 7.89 (d, 1H, J = 8.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.6, 83.1, 117.2, 120.5, 133.9, 142.5, 159.5, 171.1. IR (neat): 2934, 2559, 1690 cm^{-1}. Anal. calcd. for $C_8H_7IO_3$: C, 34.56; H, 2.54. Found: C, 34.37; H, 2.71.

3-Methoxy-6-thiomethylbenzoic Acid (8e). See general procedure. After recrystallization (*n*-heptane/ethyl acetate), the acid **8e** was obtained was a brown solid (0.121 g, 61%) (mp 144−146 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.48 (s, 3H), 3.89 (s, 3H), 7.09 (dd, 1H, J = 8.8 Hz and J = 2.8 Hz), 7.23 (d, 1H, J = 8.8 Hz), 7.65 (d, 1H, J = 2.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 16.8, 56.0, 116.9, 121.1, 127.3, 127.5, 134.9, 156.9, 171.1. IR (neat): 2970, 2567, 1673 cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_9H_{10}O_3S$ ($M^{+\bullet}$): 198.0351. Found: 198.0358.

General Procedure for the Preparation of 2-Substituted 4-Methoxybenzoic Acids (9a-f). Preparation of 3-Hydroxy-5-methoxyisobenzofuran-1(3*H*)-one (15) and 5-Methoxy-3-phenylisobenzofuran-1(3*H*)-one (16) (route F). To a stirred solution of a 1:1 *s*-BuLi/TMEDA complex (11 mmol) in anhydrous THF at −78 °C was added dropwise under argon the recrystallized *p*-anisic acid (**3**) (0.76 g, 5 mmol) dissolved in dry THF (5 mL). After 2 h at this temperature, the mixture was treated with an excess of the appropriate electrophile (20 mmol) dissolved in THF. The resulting solution was then slowly allowed to warm to ambient temperature, and water was added. The aqueous layer was washed with diethyl ether (2 × 30 mL), shaken, and acidified with 2 M HCl. The mixture was then diluted with diethyl ether, and the organic layer was separated and dried with $MgSO_4$.

4-Methoxy-2-methylbenzoic Acid (9a). According to the general procedure, the recrystallized *p*-anisic acid (**3**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by MeI (2.84 g, 20 mmol). Workup followed by recrystallization (heptane/ethyl acetate) afforded **9a** (0.61 g, 73%) as a white solid: mp 177−178.5 °C (lit.[42] 176−178 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.52 (s, 3H), 3.80 (s, 3H), 6.82 (d, 1H, J = 8.4 Hz), 6.84 (s, 1H), 7.84 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 22.8, 56.3, 112.2, 118.1, 123.0, 134.5, 144.3, 163.8, 168.9. IR (neat): 2927, 1661, 1566, 1450, 1285, 1158 cm^{-1}.

4-Methoxy-2-trimethylsilylbenzoic Acid (9b). To a solution of LTMP (9 mmol) in THF (20 mL) at −78 °C were added successively TMSCl (1.38 mL, 10.5 mmol) in THF (5 mL) and *p*-anisic acid (**3**) (0.46 g, 3 mmol) in THF (3 mL). After being warmed gradually to rt for 4 h, the solution was allowed to warm to rt. Aqueous 2 M NaOH was added until the pH reached 10. The aqueous layer was washed with diethyl ether, acidified with aqueous 4M HCl, and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by colum chromatography on silica gel (cyclohexane/diethyl ether 90:10) to give **9b** (0.54 g, 80%) as a white solid: mp 134−136.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.35 (s, 9H), 3.89 (s, 3H), 6.92 (dd, 1H, J = 8.6 Hz and J = 2.6 Hz), 7.23 (d, 1H, J = 2.6 Hz), 8.19 (d, J = 8.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 0.54, 54.9, 112.4, 121.8, 125.9, 133.3, 146.3, 162.4, 172.8. IR (neat): 2945, 1676, 1584, 1416, 1316, 1235. cm^{-1}. HRMS (EI) *m*/*z* calcd. for $C_{11}H_{16}O_3Si$ ($M^{+\bullet}$): 224.0869. Found: 224.0880.

2-Chloro-4-methoxybenzoic Acid (9c). According to the general procedure, the recrystallized *p*-anisic acid (**3**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by hexachloroethane (4.73 g, 20 mmol). Workup in the usual manner followed by recrystallization (heptane/ethyl acetate) afforded **9c** (0.70 g, 75%) as a white solid: mp 111.5−112.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.86 (s, 3H), 6.97 (dd, 1H, J = 8.8 Hz and J = 2.5 Hz), 7.09 (d, 1H, J = 2.5 Hz, 1H), 7.83 (d, 1H, J = 8.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 56.3, 113.5, 116.5, 122.7, 133.5, 134.5, 162.4, 166.3. IR (neat): 2945, 1661, 1595, 1406, 1272, 1026 cm^{-1}. Anal. calcd. for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found: C, 51.56; H, 3.81

2-Bromo-4-methoxybenzoic Acid (9d) and 3-Bromo-4-methoxybenzoic Acid (20). According to the general procedure, the recrystallized *p*-anisic acid (**3**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by dibromotetrachloroethane (6.51 g, 20 mmol). Workup in the usual manner followed by recrystallization (heptane/ethyl acetate) led to a mixture of 2-bromo-4-methoxybenzoic acid (**9d**) and 3-bromo-4-methoxybenzoic acid (**20**) (54%) that could not be separated by chromatography (**9d**:**20** 48/52). **9d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.97 (s, 3H), 7.08 (dd, 1H, J = 8.8 Hz and J = 2.5 Hz), 7.20 (d, 1H, J = 8.8 Hz), 7.36 (d, 1H, J = 2.5 Hz, 1H). **20**:[42,58] ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.97 (s, 3H), 7.00 (dd, 1H, J = 8.9 Hz and J = 2.5 Hz), 7.92 (d, 1H, J = 8.8 Hz), 7.94 (d, 1H, J = 2.5 Hz, 1H).

2-Iodo-4-methoxybenzoic Acid (9e). According to the general procedure, the recrystallized *p*-anisic acid (**3**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by iodine (5.07 g, 20 mmol). Workup in the usual manner followed by recrystallization (chloroform) afforded **9e** (0.98 g, 71%) as a brown solid: mp 174−176 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.83 (s, 3H), 7.06 (dd, 1H, J = 8.6 Hz and J = 2.5 Hz), 7.52 (d, 1H, J = 2.5 Hz), 7.81 (d, 1H, J = 8.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 55.7, 96.0, 113.7, 127.2, 131.3, 132.1, 161.4, 166.9. IR (neat): 2974, 2646, 1681, 1556, 1406, 1286 cm^{-1}. Anal. calcd. for $C_8H_7IO_3$: C, 34.56; H, 2.53. Found: C, 34.89; H, 2.51.

4-Methoxy-2-(methylthio)benzoic Acid (9f). According to the general procedure, the recrystallized *p*-anisic acid (**3**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by dimethyl disulfide (1.88 g, 20 mmol). Workup in the usual manner followed by recrystallization (chloroform) afforded **9f** (0.76 g, 76%) as a

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white solid: mp 118−120 °C.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.38 (s, 3H), 3.85 (s, 3H), 7.76 (m, 2H), 7.90 (d, 1H, J = 9.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.7, 55.4, 108.6, 109.8, 119.3, 133.3, 145.3, 162.3, 166.8. IR (neat): 3020, 2565, 1672, 1550, 1483, 1283 cm^{-1}.

3-Hydroxy-5-methoxyisobenzofuran-1(3*H*)-one (15). According to the general procedure, the recrystallized *p*-anisic acid (**3**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by DMF (1.46 g, 20 mmol) (reverse addition). Workup in the usual manner followed by recrystallization (chloroform) afforded **15** (0.58 g, 64%) as a white solid: mp 134−136 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.98 (s, 3H), 6.54 (s, 1H), 7.16 (m, 1H), 7.72 (d, 1H, J = 9.2 Hz), 8.12 (d, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 55.4, 97.3, 107.6, 117.7, 118.6, 126.1, 150.3, 164.5, 168.0. IR (neat): 3270, 1727, 1621, 1491, 1294 cm^{-1}. Anal. calcd. for C_9H_8O4: C, 60.00; H, 4.48. Found: C, 59.82; H, 4.38.

(59) CAS number: 72856-74-7. Robertson, D. W.; Beedle, E. E.; Krushinski, J. H.; Don Pollock, G.; Wilson, H.; Wyss, V. L.; Hayes, J. S. *J. Med. Chem.* **1985**, *28*, 717. The melting point is not reported.

5-Methoxy-3-phenylisobenzofuran-1(3*H*)-one (16). According to the general procedure, the recrystallized *p*-anisic acid (**3**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by benzaldehyde (2.12 g, 20 mmol). Workup in the usual manner followed by recrystallization (chloroform) afforded **16** (0.830 g, 69%) as a white solid: mp 124−126 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 3.83 (s, 3H), 6.61 (s, 1H), 6.71 (d, 1H, J = 1.5 Hz), 7.04 (dd, 1H, J = 8.9 and J = 2.5 Hz), 7.25−7.30 (m, 2H), 7.37−7.41 (m, 3H), 7.86 (d, 1H, J = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 55.8, 82.5, 106.7, 116.8, 127.1, 129.4, 136.7, 153.0, 165.4, 170.6. IR (neat): 2943, 1749, 1599, 1487, 1293, 1248. cm^{-1}. Anal. calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.66; H, 5.03.

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