

Metallation reactions XXII¹. Regioselective metallation of (trifluoromethyl)(alkylthio)benzenes

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Abstract

The metallation reactions of (trifluoromethyl)(alkylthio)benzenes with organolithium reagents and with the butyllithium/potassium *tert*-butoxide superbasic mixture are here described. The results, according to the theoretical calculations of energy minima, show the monometallation regiochemistry is directed by the sulphur atom. On the other side, the bimetallation, that can be performed only on methylthio derivatives, depends on the organometallic reagent employed. Using butyllithium the stronger coordinative power of sulphur prevails and products metallated in *ortho* and *alpha* positions to this atom are mainly formed. With the more basic *sec*-butyllithium and with the superbase, because of mutual competition between the thioalkyl and trifluoromethyl groups, mixtures of products, coming from metallation in the *ortho* position to the trifluoromethyl group and in the *alpha* position of the thiomethyl group, are obtained. In addition, products coming from substitution *ortho, alpha* to the thiomethyl group are also formed. All mono- and bimetalated intermediates showed to be good synthons for the synthesis of fluoro- and (trifluoromethyl)-substituted benzothiophenes and (trifluoro-methyl)benzenes substituted on the thioalkylic chain and/or on the ring.

Keywords: Organolithium; Superbases; Metallation; Trifluoromethyl(alkylthio)arenes; Benzothiophenes

1. Introduction

The direct lithiation of aromatics is a useful synthetic process to prepare polyfunctionalized molecules. Nowadays this method is still an object of study and application in organic chemistry [2–12].

In connection with our previous studies [13,1], in this work we extended our research to (alkylthio)(trifluoromethyl)benzenes, to investigate the regiochemistry of the organometallic attack and verify the synthetic power of these substrates.

This research is justified by the remarkable growth of the fluorinated compounds chemistry in recent years, because of their employment in the biological, pharmacological and new materials field [14–29]. In fact, several compounds containing the fluorine atom or the trifluoromethyl group show a biological activity as antimycotics, insecticides, psychotropics, antihypertensive agents, diuretics and as anticancer and antiviral agents.

The literature reports a detailed study of the regiochemistry of the metallation of fluoroanisoles and fluoro- or (trifluoromethyl)-substituted benzenes, which showed a regioselectivity controlled by the organometal used [11,23,29–36]. On the other hand there are only few reports on similar molecules containing the thioalkyl function.

2. Results and discussion

The compounds reported in this work were reacted with different metallating reagents (butyllithium, *sec*-butyllithium, superbasic mixture obtained mixing butyllithium and potassium *tert*-butoxide). All the metallated intermediates were quenched with iodomethane and analysed by GC/MS.

The results show that 4-(methylthio)-1-(trifluoromethyl)benzene (**1a**) (Table 1 and Scheme 1), treated with one equivalent of butyllithium for 1 or 4 h, affords, after quenching with iodomethane, almost quantitatively the unreacted starting material with traces of three monometallated products (**3**, **4**, **5**) and one bimetalated

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¹ Dedicated to Professor F. Montanari on the occasion of his 70th birthday. For Part XXI, see Ref. [1].

product (**6**). When the reaction is performed using two equivalents of butyllithium and quenching with iodomethane after 1 h, the starting material (**22**%), and the products **3** (**28**%), **4** (**21**%), **5** (**17**%) and **6** (**12**%) are detected. Quenching after 4 h leads to a 9% yield of **1a**, 37% of **3**, 12% of **4**, 18% of **5** and 20% of **6**; also, another product **7** (**13**%) is formed by metallation of the thiomethyl group and of the position *ortho* to the trifluoromethyl moiety. Using four equivalents of butyllithium, after 1 h, three monosubstituted products, **3**, **4**, **5**, and two disubstituted products, **6** and **7**, can be detected; **6** is present in a 54% amount while there are

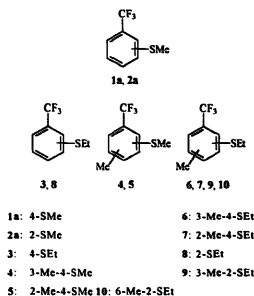
only traces of the starting material. After 4 h, beside traces of **1a**, we found the monolithiated **3** (**11**%), the dilithiated **6** (**69**%) and **7** (**17**%). Operating with two equivalents of *sec*-butyllithium or superbase we found almost exclusively **3**; with four equivalents of the same reagents, a mixture of **6** and **7** was formed.

Analogously, from reaction of 2-(methylthio)-1-(trifluoromethyl)benzene (**2a**) (Table 1 and Scheme 1) with two equivalents of butyllithium or *sec*-butyllithium or superbase we obtain the monosubstituted product together with small amounts of the bisubstituted product **9**; the latter becomes the main product using three

Table 1
Metallation of (alkylthio)(trifluoromethyl)benzenes (**1a–b**, **2a–b**)^a

Entry	RM (equivalent)	T (°C)	t (min)	Starting material (%)	α -S (%)	<i>o</i> -S (%)	<i>o</i> -CF ₃ (%)	α , α -S (%)	α -S- <i>o</i> -CF ₃ (%)	<i>o</i> -S- <i>o</i> -CF ₃ (%)
1a	BuLi (1)	10	60	95	tr	tr	tr	tr		
1a	BuLi (1)	10	240	91	tr	tr	tr	tr		
1a	BuLi (2)	10	60	22	28	21	17	12		
1a	BuLi (2)	10	240	9	37	12	18	20		13
1a	BuLi (4)	10	60	3	11	8	4	54		20
1a	BuLi (4)	10	240	3	11			69		17
1a	<i>sec</i> -BuLi (1)	-50	240	99	< 1					
1a	<i>sec</i> -BuLi (2)	-50	240	18	80	tr	tr	tr		tr
1a	<i>sec</i> -BuLi (4)	-50	240	< 1	10			48		40
1a	LICKOR (1)	-70	360	90	8	2				
1a	LICKOR (2)	-70	360	10	75	15				
1a	LICKOR (4)	-70	360	< 1	6	16		47		31
2a	BuLi (1)	10	240	~ 100						
2a	BuLi (2)	10	240	21	64			15		
2a	BuLi (3)	10	240	9	32			58		
2a	BuLi (4)	10	240	5	19			46		30
2a	<i>sec</i> -BuLi (1)	-50	240	~ 100						
2a	<i>sec</i> -BuLi (2)	-50	240	< 1	99					
2a	<i>sec</i> -BuLi (4)	-50	240	< 1	11			45		43
2a	LICKOR (1)	-70	360	~ 90	10					
2a	LICKOR (2)	-70	360	8	90			tr		tr
2a	LICKOR (4)	-70	360	5	84			6		5
1b	BuLi (1)	10	240	~ 100		tr	tr			
1b	BuLi (2)	10	240	6		83	11			
1b	BuLi (4)	10	240	< 1		84	15			
1b	BuLi (8)	10	240	< 1		86	13			
1b	<i>sec</i> -BuLi (1)	-50	240	~ 100						
1b	<i>sec</i> -BuLi (2)	-50	240	14		46	40			
1b	<i>sec</i> -BuLi (4)	-50	240	10		49	41			
1b	LICKOR (1)	-70	360	~ 100						
1b	LICKOR (2)	-70	360	10		45	45			
1b	LICKOR (4)	-70	360			40	40			20
1b	LICKOR (8)	-70	360			41	37			22
2b	BuLi (1)	10	240	~ 100						
2b	BuLi (2)	10	240	4		96				
2b	BuLi (4)	10	240	< 1		94				6
2b	BuLi (8)	10	240	< 1		90				10
2b	<i>sec</i> -BuLi (1)	-50	240	~ 100						
2b	<i>sec</i> -BuLi (2)	-50	240	10		54	36			
2b	<i>sec</i> -BuLi (4)	-50	240	8		55	37			
2b	LICKOR (1)	-70	360	~ 100						
2b	LICKOR (2)	-70	360	< 1	10	45	45			
2b	LICKOR (8)	-70	360	< 1	12	45	43			

^a The metallation products were quenched with iodomethane; the yields were determined by GC analyses; tr = traces; LICKOR = equimolar mixture of butyllithium and potassium *tert*-butoxide.



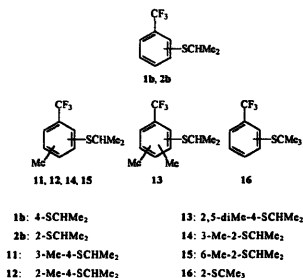
Scheme 1.

equivalents of butyllithium. With four equivalents of the same reagent or *sec*-butyllithium a mixture of the two disubstituted products **9** and **10** is formed.

By reaction of 4-(isopropylthio)-1-(trifluoromethyl)benzene (**1b**) (Table 1 and Scheme 2) with butyllithium (two or more molar equivalents) the monosubstituted product **11** together with small amounts of **12** are formed. With two or more molar equivalents of *sec*-butyllithium or superbase **11** and **12** were formed in almost equimolar amounts, while with four molar equivalents of superbase, beside **11** and **12**, we found the disubstituted product **13** (ca. 20%).

Analogous results were obtained in the case of 2-(isopropylthio)-1-(trifluoromethyl)benzene (**2b**) (Table 1 and Scheme 2): using butyllithium the monosubstituted product **14** was obtained, whereas with *sec*-butyllithium or with superbases a mixture of the two monosubstituted products **14** and **15** was formed. With superbases a small amount of **16** (10%), coming from the substitution of the hydrogen *alpha* to the thioether group, is also formed.

The results show that in the reactions between trifluoromethyl compounds and butyllithium the sulphur atom



Scheme 2.

controls more than 80% of the reactive sites in the mono- and in the bimetalations. This supports the fact that butyllithium is able to act by complexation. In fact, complexation can occur through the sulphur atom of the alkylthio group, which thus has a directing power stronger than the trifluoromethyl group, which is not capable of coordination. This group is characterized only by a low electronegativity because of the interposition of a carbon atom between the halogens and the ring: thus, an acid–base interaction is more difficult using butyllithium that is less basic than *sec*-butyllithium and superbase; the contrary occurs in the fluoro derivatives bearing the halogen atom directly linked to the ring [13]. Further evidence of this is given by the results obtained with the more basic *sec*-butyllithium and with superbases. From the reactions of *sec*-butyllithium with **1b** or **2b** it is evident that the strong competition between the two *ortho* sites (to the trifluoromethyl and the thioalkyl group) allows formation of isomeric mixtures of almost equal amounts of the two products. Clearly, the remarkable basicity of this organolithium is able to promote hydrogen-abstraction even from the less acidic sites; so, even the low inductive effect of the trifluoromethyl group can work, without any coordinative aid. The same occurs in the bimetalation of **1a** and **2a**, while in their monometallation the higher acidity of the thiomethyl group, in addition with the stabilization of the corresponding carbanion by the sulphur atom, prevails.

Similar considerations can be made to explain the results obtained with the superbases.

All these results are also in agreement with the data obtained by MMX calculations (MMX force field as in PCMODEL, Serena Software, Bloomington, IN, see Ref. [37]), which agree well with the experimental data.

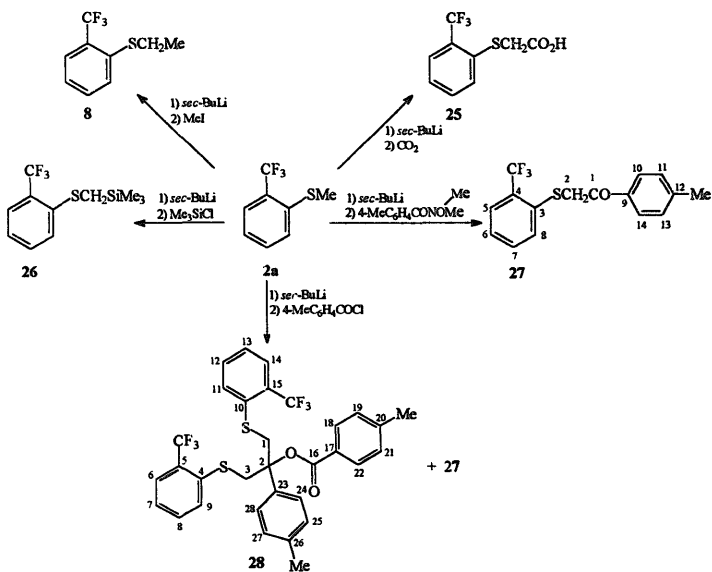
Another remarkable result is that significant amounts of bimetalated products are accessible only from methylthio derivatives. On the other hand, the isopropylthio derivatives always gave only small yields of bimetalated products even working with a large excess of organolithium or superbase.

It is also noticeable that when the reaction of **1a** is quenched after 1 h, it is possible to reveal the products of monometallation in *ortho* to the sulphur atom, while their amount decreases using longer reaction times, as previously noticed [38–40].

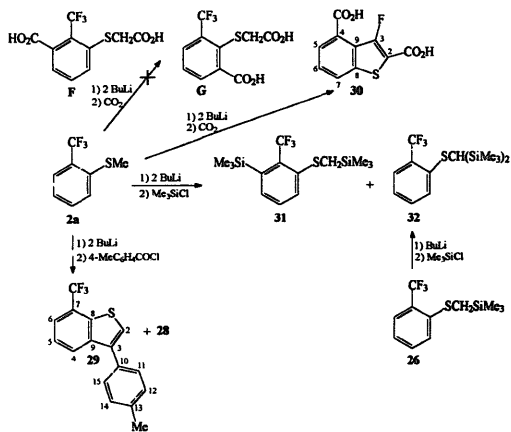
The isopropylthio derivative **2b** gave an unexpected result: it was found the *tert*-butyl product **16** probably derived from a rather unstable secondary carbanion.

Another remarkable fact is the necessity to use excess of organometallic reagent to carry out the metallation. This phenomenon already noticed by Quéguiner and coworkers [41] in pyridazinic derivatives can be explained by competitive complexation.

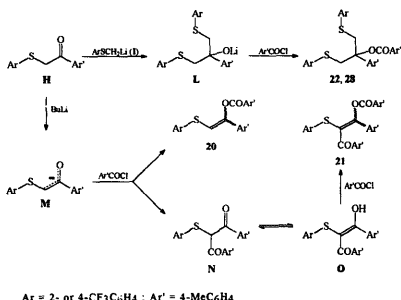
It is significant that **2a**, in the monometallation reactions, affords only the product metallated in the *alpha*



Scheme 5.



Scheme 6.



Scheme 7.

(18) acids besides the already mentioned 3. Treating the bimetalated intermediate with acyl halides the benzothio-phenic derivative 19 was obtained (always with the by-products 20, 21, 22).

Starting from 1b and 2b (Scheme 4) it was possible to prepare products substituted in *ortho* to the thioether group, as shown by the formation of 11, 14 and 23, 24.

Even 2a proved to be a useful synthon to prepare several functionalized compounds. In fact, the monometallation (Scheme 5) allows one to prepare derivatives by substitution of the thiomethyl hydrogen, as shown by the attainment of 8, 25–28. It is noteworthy that, employing the *N*-methoxy-*N*-methylamide of the 4-methoxybenzoic acid as electrophile [43], the ketone 27 has been prepared in satisfactory yield; from the corresponding acyl halide the main product is 28.

The results of the bimetalations are more complex (Scheme 6). These reactions often give isomeric mixtures that are easily separable by chromatography.

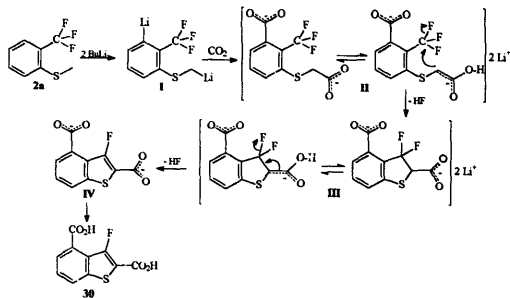
Quenching the metallated mixture of 2a with 4-methylbenzoyl chloride, the product 29 is obtained beside a small amount of 28. Using carbon dioxide as electrophile we obtained the benzothiophenic derivative 30 instead of the expected bicarboxylic acids F and G. With chlorotrimethylsilane we prepared the bis- α -substituted 32 beside the expected 31, while no trace of the disilylated product arising from substitution of hydrogens in the *alpha* and *ortho* positions to the thiomethyl group was detected.

The formation of 20, 21, 22 and 28 (Scheme 7) can be explained by the primary formation of the ketone H from the attack of the acyl chloride to the monolithiated intermediate I, followed by a further nucleophilic attack by another molecule of I to give the alkoxide L, that finally reacts with another molecule of acyl chloride to give 22 or 28. Otherwise, the same ketone H could be converted into the enolate anion M by the organometallic reagent. Then M could react with the acyl chloride to give the *O*-acylated derivative 20 or the *C*-acylated N. The last is likely in equilibrium with its tautomer O, that in its turn could react with the acyl chloride to give 21.

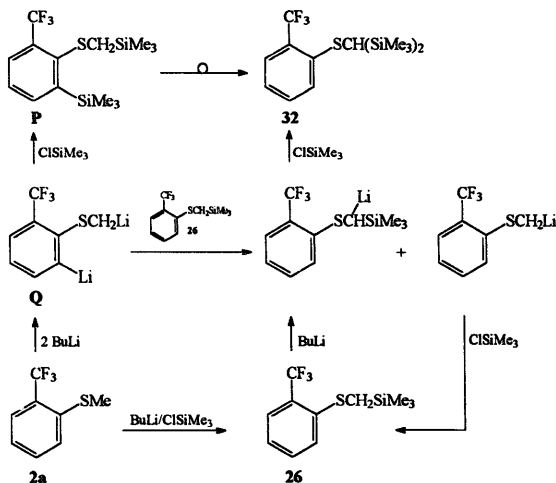
The formation of the benzothiophenes 19 and 29 is explained on the basis of a first nucleophilic attack to the acyclic carbon by one of the two lithiated sites followed by a second nucleophilic intramolecular attack to the carbonyl carbon atom by the other lithiated site [44].

The formation of 30 can be explained by a primary intramolecular cyclization (Scheme 8), anchimerically assisted by the carboxylate anion in *ortho* to the trifluoromethyl group [45], owing to a nucleophilic substitution of the fluorine atom by the SCH[−] anion to give the benzothiophenic intermediate III, that aromatizes to give IV, that, after acidification is transformed in 30.

Finally, the presence of 32 can be explained (Scheme 9) by an *ortho*–*alpha* shift of the trimethylsilyl group in



Scheme 8.



Scheme 9.

the **P** intermediate (not isolated), or by a further metallation on the monosilylated **26** by the organolithium in excess (or by the aryllithium **Q** primarily formed) followed by final quenching by the chlorotrimethylsilane. The last hypothesis is supported by the possibility of preparing **32** by metallation/silylation of **26**, isolated from the monometallation reaction.

The identification of all the products was performed by interpretation of the mass and NMR spectra or by comparison with authentic samples.

For what concerns the product of the monometallation of **1a**, the mass spectra of the three isomers **3**, **4** and **5** show the same molecular ion at m/e 206 that is also the base peak. The compound **3** differs from **4** and **5** for the presence of the peak at m/e 178 (60%) because of the loss of ethylene. The identification of **4** and **5** is based on the fact that **5** shows a peak at m/e 191 ($\text{M}^+ - \text{CH}_3$) less intense than **4**, while the peak at m/e 173 ($\text{M}^+ - \text{SH}$) is stronger in **5** than in **4**. This agrees with what is observed in the 2-methyl- and 3-methyl-1-(methylthio)benzene [46].

The identification of the products **6** and **7**, which show the same molecular ion and base peak at m/e 220, was made considering that **6** shows a peak at m/e 191 ($\text{M}^+ - \text{C}_2\text{H}_5$) higher than at m/e 192 ($\text{M}^+ - \text{C}_2\text{H}_4$) and that in the spectrum of **7** the peak at m/e 191 is almost nonexistent. This can be explained by the fact that in **7** the loss of ethylene is prevalent on the loss of ethyl because this process leads to the formation of a neutral fragment and a strongly stabilized ion. On the

contrary, in the product **6** the loss of the ethyl radical prevails, because of the stabilization of the thionic ion by the *ortho* methyl group. Moreover, this fragmentation is probably favoured by the formation of the tropylium ion derived by a hydrogen transfer from methyl to sulphur. To confirm our hypothesis we prepared the bicarboxylic acid **18**, the main isomer formed, whose ^{13}C NMR decoupled spectrum shows at δ 126.02 ($^3J_{\text{CF}} = 2.92$ Hz) and at δ 127.44 ($^3J_{\text{CF}} = 4.87$ Hz) two quartets corresponding to the aromatic carbons C-3 and C-5 respectively. In the coupled spectrum both the quartets are splitted in two doublets of multiplets because of the coupling to the *ipso* proton ($^1J_{\text{CH}} = 166.05$ Hz for the C-3 and $^1J_{\text{CH}} = 164.77$ Hz for the C-5) and this shows that the carboxy group is in the *ortho* position to the sulphur atom.

For what concerns the products derived from the metallation of **2a**, the structure of **8** was determined by comparison with an authentic sample, while the distinction between **9** and **10** was made by mass spectra analysis. In fact, as observed for **1a**, when the methyl group is in *ortho* to the SC_2H_5 , the loss of an ethyl radical is favoured, while with a methyl group in *meta* the loss of ethylene prevails. In fact, **9** shows a peak at m/e 192 ($\text{M}^+ - \text{C}_2\text{H}_4$) with a relative abundance of 14.3% and another one at m/e 191 ($\text{M}^+ - \text{C}_2\text{H}_5$) with abundance of 3.2%; in the product **10** the corresponding peaks show a relative abundance of 14% and 37% respectively.

We could not identify the isomers **11** and **12** by their

mass spectra because both showed the same fragmentations and the same abundancies. Owing to this fact we prepared the carboxylic acid **23**, the main isomer, whose structure was determined by ^{13}C NMR spectroscopy similarly to that described for the acid **18** (see Section 3).

Finally, for what concerns the products derived from the metallation of **2b**, which show the same molecular ion at m/e 234, the structure of **16** was determined by the presence of the peak at m/e 178 ($\text{M}^+ - \text{C}_4\text{H}_8$) and at m/e 57 (C_4H_7^+). The identification of **14**, derived by the reaction with butyllithium, was made preparing the carboxylic acid **24**, whose structure was determined by ^{13}C NMR spectroscopy (see Section 3). In consequence, the product **15** that shows a different GC retention time and a different spectrum from **14**, has the methyl group in *ortho* to the trifluoromethyl.

3. Experimental details

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. IR spectra were recorded on a Perkin-Elmer 1310 grating spectrophotometer. Analyses by HPLC were carried out with a Waters 600 HPLC equipped with a UV Gilson 116 detector and a Spherisorb 5μ ODS2 column ($25\text{ cm} \times 4.6\text{ mm}$). The GC-MS analyses were performed at 70 eV with a Hewlett Packard 5989A GC-MS system with HP 5890 GC fitted with a capillary column ($50\text{ m} \times 0.2\text{ mm}$) packed with DH 50.2 Petrocol ($0.50\text{ }\mu\text{m}$ film thickness). All flash chromatographies were performed on silica G60 (Merck) columns. Microanalyses were carried out with a Carlo Erba 1106 elemental analyser. Melting points were obtained on a Kofler hot stage microscope and are uncorrected.

Commercially available reagent-grade starting materials and solvents were used. Solutions of butyllithium in hexane were obtained from Aldrich Chemical Company and were analysed by the Gilman double titration method before use [47].

3.2. Starting materials

3.2.1. 4-(Methylthio)-1-(trifluoromethyl)benzene (**1a**)

A mixture of 4-chloro-1-(trifluoromethyl)benzene (7.6 g, 42 mmol), sodium methanethiolate (3.1 g, 45 mmol) and anhydrous *N,N*-dimethylformamide (100 ml) was stirred under nitrogen at $40\text{--}50^\circ\text{C}$ for 20 h, then allowed to cool and added to a saturated solution of aqueous sodium chloride. The organic product was extracted with diethyl ether, the ethereal layer was separated and dried (CaCl_2), the solvent evaporated

and the product purified by flash-chromatography with light petroleum as eluent. Yield 86%; m.p. $36\text{--}37^\circ\text{C}$; ^1H NMR (CDCl_3) δ : 2.58 (s, 3H, SCH_3), 7.37 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H); ^{13}C (^1H) NMR (CDCl_3) δ : 14.94 (q, CH_3), 124.22 (qd, CF_3 , $^1J_{\text{CF}} = 270.1\text{ Hz}$), 125.49 (dd, C-3 and C-5, $^2J_{\text{CF}} = 3.07\text{ Hz}$), 125.51 (m, C-2 and C-6), 126.72 (qm, C-1, $^2J_{\text{CF}} = 32.4\text{ Hz}$), 143.82 (m, C-4). EI-MS: $m/e = 192$ (100%, M^+), 177 (9.6%, $\text{M}^+ - \text{CH}_3$), 173 (10.1%, $\text{M}^+ - \text{F}$), 171 (9.5%, $\text{M}^+ - \text{HF} - \text{H}$), 159 (35.4%, $\text{M}^+ - \text{SH}$), 157 (14.5%, $\text{M}^+ - \text{CH}_3 - \text{HF}$), 145 (8.0%, $\text{M}^+ - \text{SCH}_3$), 127 (7.5%, $\text{C}_6\text{H}_4\text{S}^+$), 108 (7.7%, $\text{C}_6\text{H}_3\text{S}^+$), 69 (11.2, CF_3^+), 46 (20.9, CH_2S^+), 45 (21.1, CHS^+). Elemental analysis. Found: C, 49.85; H, 3.62; S, 16.53. $\text{C}_6\text{H}_4\text{F}_3\text{S}$ (192.2) calcd.: C, 49.99; H, 3.67; S, 16.68%.

3.2.2. 4-[(1-Methylethyl)thio]-1-(trifluoromethyl)benzene (**1b**)

A mixture of 4-chloro-1-(trifluoromethyl)benzene (7.6 g, 42 mmol), sodium 2-propanethiolate (4.4 g, 45 mmol) and anhydrous *N,N*-dimethylformamide (100 ml) was stirred under nitrogen at $40\text{--}50^\circ\text{C}$ for 20 h, then allowed to cool, added to a saturated solution of aqueous sodium chloride and worked up as described above. The product was purified by flash-chromatography with light petroleum-diethyl ether (9:1) as eluent. Yield 78%. Oil, n_D^{20} 1.4620; ^1H NMR (CDCl_3) δ : 1.45 (d, 6H, C_2H_5), 3.66 (m, 1H, SCH_2), 7.82 (m, 4H, Ar-H); ^{13}C (^1H) NMR (CDCl_3) δ : 22.87 (qm, CH_3), 37.19 (dm, CH), 124.15 (qm, CF_3 , $^1J_{\text{CF}} = 270.1\text{ Hz}$), 125.54 (dm, C-2 and C-6, $^2J_{\text{CF}} = 3.67\text{ Hz}$), 127.88 (qm, C-1, $^2J_{\text{CF}} = 32.17\text{ Hz}$), 129.62 (dd, C-3 and C-5), 141.52 (t, C-4). EI-MS: $m/e = 220$ (54.8%, M^+), 205 (4.8%, $\text{M}^+ - \text{CH}_3$), 201 (4.5%, $\text{M}^+ - \text{F}$), 178 (93.5%, $\text{M}^+ - \text{C}_3\text{H}_6$), 158 (24.2%, $\text{M}^+ - \text{C}_3\text{H}_6 - \text{HF}$), 108 (8.1%, $\text{C}_6\text{H}_4\text{S}^+$), 69 (8.3%, CF_3^+), 43 (100%, C_3H_7^+). Elemental analysis. Found: C, 54.44; H, 4.98; S, 14.41. $\text{C}_{10}\text{H}_{11}\text{F}_3\text{S}$ (220.2) calcd.: C, 54.53; H, 5.03; S, 14.56%.

3.2.3. 2-(Methylthio)-1-(trifluoromethyl)benzene (**2a**)

A mixture of 2-chloro-1-(trifluoromethyl)benzene (7.6 g, 42 mmol), sodium methanethiolate (3.1 g, 45 mmol) and anhydrous *N,N*-dimethylformamide (100 ml) was stirred under nitrogen at $40\text{--}50^\circ\text{C}$ for 20 h, then allowed to cool, added to water and worked up as described above. The product was purified by flash-chromatography with light petroleum as eluent. Yield 92%. Oil, n_D^{20} 1.4990; ^1H NMR (CDCl_3) δ : 2.49 (s, 3H, SCH_3), 7.20 (t, 1H, H-4 or H-5), 7.35 (d, 1H, H-3 or H-6), 7.46 (t, 1H, H-4 or H-5), 7.61 (d, 1H, H-3 or H-6); ^{13}C (^1H) NMR ($\text{DMSO}-d_6$) δ : 15.15 (q, CH_3), 124.19 (qd, CF_3 , $^1J_{\text{CF}} = 271.87\text{ Hz}$), 124.87 (dd, C-5), 125.53 (dm, C-6, $^2J_{\text{CF}} = 5.47\text{ Hz}$), 126.05 (qt, C-1, $^2J_{\text{CF}} = 29.7\text{ Hz}$), 127.18 (dd, C-3), 132.96 (dd, C-4), 138.17 (m, C-2). EI-MS: $m/e = 192$ (100%, M^+), 177 (8.8%, $\text{M}^+ - \text{CH}_3$), 171 (8.6%, $\text{M}^+ - \text{HF} - \text{H}$), 159 (25.8%,

$M^+ - SH$), 157 (12.0%, $M^+ - CH_3 - HF$), 152 (9.6%, $M^+ - 2HF$), 145 (6.4%, $M^+ - SCH_3$), 127 (10.4%, $C_6H_4FS^+$), 109 (4.3%, $C_6H_5S^+$), 108 (8.0%, $C_6H_4S^+$), 69 (9.6%, CF_3^+), 46 (20.9%, CH_2S^+), 45 (17.7%; CHS^+). Elemental analysis. Found: C, 49.91; H, 3.63; S, 16.55. $C_8H_7F_3S$ (192.2) calcd.: C, 49.99; H, 3.67; S, 16.68%.

3.2.4. 2-[(1-Methylethyl)thio]-1-(trifluoromethyl)-benzene (2b)

A mixture of 2-chloro-1-(trifluoromethyl)benzene (7.6 g, 42 mmol), sodium 2-propanethiolate (4.4 g, 44 mmol) and anhydrous *N,N*-dimethylformamide (100 ml) was stirred under nitrogen at 40–50°C for 20 h and worked up as described above. The product was purified by flash-chromatography with light petroleum as eluent. Yield 72%. Oil, n_D^{20} 1.4924; 1H NMR ($CDCl_3$) δ : 1.30 (d, 6H, CH_3), 3.46 (m, 1H, CH), 7.27 (t, 1H, H-4 or H-5), 7.44 (t, 1H, H-4 or H-5), 7.55 (d, 1H, H-3 or H-6), 7.64 (d, 1H, H-3 or H-6); ^{13}C NMR ($CDCl_3$) δ : 22.78 (qm, CH_3), 38.84 (dm, CH), 123.75 (qd, CF_3 , $^1J_{CF} = 271.87$ Hz), 126.23 (dd, C-4), 126.70 (dm, C-6, $^3J_{CF} = 5.45$ Hz), 131.07 (qm, C-1, $^2J_{CF} = 29.7$ Hz), 131.69 (dd, C-5), 133.29 (dd, C-3), 135.67 (m, C-2). EI-MS: $m/e = 220$ (37.5%, M^+), 205 (2.6%, $M^+ - CH_3$), 178 (48.1%, $M^+ - C_2H_5$), 177 (5.9%, $M^+ - C_3H_7$), 159 (11.2%, $M^+ - C_3H_7 - F$), 158 (100%, $M^+ - C_2H_5 - HF$), 157 (9.8%, $M^+ - C_3H_7 - HF$), 145 (2.5%, $M^+ - SC_2H_5$), 133 (2.9%, $C_6H_4F_2^+$), 114 (11.2%, $C_6H_4F_2^+$), 108 (5.2%, $C_6H_5S^+$), 69 (5.3%, CF_3^+), 43 (45.4%, $C_3H_7^+$). Elemental analysis. Found: C, 54.41; H, 4.95; S, 14.42. $C_{10}H_{11}F_3S$ (220.2) calcd.: C, 54.53; H, 5.03; S, 14.56%.

3.3. Authentic samples

3.3.1. 2-(Ethylthio)-1-(trifluoromethyl)benzene (8)

A suspension of 2-(trifluoromethyl)benzenamine (5 g, 33 mmol), water (60 ml) and concentrated hydrochloric acid (80 ml) was diazotized at 0–5°C with an aqueous solution of sodium nitrite (2.5 g, 36 mmol). The resulting mixture was added to a solution of potassium ethyl xanthogenate (9.9 g, 69 mmol) keeping the reaction at 70–80°C. When the addition was complete the mixture was stirred for ca. 1 h at the same temperature. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic extracts were evaporated. The residue was refluxed for 6 h with a solution of potassium hydroxide (6.6 g, 118 mmol) and then treated with diethylsulphate (5 g, 33 mmol). When the addition was complete, the mixture was refluxed for ca. 1 h, cooled and poured into water. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Yield 68%. Oil, b.p. 95–96°C/17 mm Hg; n_D^{20} 1.5045; 1H NMR ($CDCl_3$) δ : 1.31 (t, 3H, CH_3), 2.97 (q, 2H, CH_2), 7.23 (m, 1H,

Ar-H), 7.44 (m, 2H, *Ar-H*), 7.61 (d, 1H, *Ar-H*); ^{13}C NMR ($CDCl_3$) δ : 13.74 (qt, CH_3), 27.92 (qq, CH_2), 123.83 (qd, CF_3 , $^1J_{CF} = 272.25$ Hz), 125.31 (dm, C-5), 126.69 (dm, C-6, $^3J_{CF} = 5.47$ Hz), 129.35 (qd, C-1, $^2J_{CF} = 30.0$ Hz), 129.89 (dd, C-3), 131.81 (dd, C-4), 136.58 (m, C-2). EI-MS: $m/e = 206$ (100%, M^+), 191 (46.6%, $M^+ - CH_3$), 178 (11.6%, $M^+ - C_2H_5$), 171 (38.3%, $M^+ - CH_3 - HF$), 158 (78.3%, $M^+ - C_2H_5 - HF$), 127 (11.1%, $C_6H_4FS^+$), 114 (95.0%, $C_6H_4F_2^+$), 108 (10.0%, $C_6H_5S^+$), 95 (7.0%, $C_6H_4F^+$), 69 (13.3%, CF_3^+), 45 (41.6%, CHS^+). Elemental analysis. Found: C, 52.33; H, 4.37; S, 15.41. $C_9H_9F_3S$ (206.2) calcd.: C, 52.42; H, 4.40; S, 15.55%.

3.4. Metallation of 1a

3.4.1. Method A

A 1.2 M solution of butyllithium in hexane (2.7 mmol) was gradually added under argon to a vigorously stirred solution of **1a** (2.5 mmol), anhydrous TMEDA (2.7 mmol) and hexane (10 ml) cooled to 10°C, and stirring was continued at the same temperature for 1 h. The resulting mixture was then treated with iodomethane (2.7 mmol), left at room temperature for 3 h and then poured into water. The organic layer was separated, the aqueous layer extracted with diethyl ether and the combined organic solutions were dried (Na_2SO_4) and analysed by GC/MS. The analysis (see Table 1) showed the presence of the starting material and traces of **3**, **4**, **5**, **6**. Similar results were obtained when the reaction time was protracted for 4 h.

When 5.4 mmol of organolithium were used, after 1 h the reaction mixture was formed by the products **3**, **4**, **5**, **6** in the ratio of 28:21:17:12 respectively; after 4 h in the mixture the products **3**, **4**, **5**, **6**, **7** were found in the ratio of 37:12:18:20:13 respectively.

When 10.8 mmol of organolithium were used, after 1 h the products **3**, **4**, **5**, **6**, **7** were detected in the ratio of 11:8:4:54:20 respectively; after 4 h **3**, **6**, **7** were detected in the ratio of 11:69:17 respectively.

3. EI-MS: $m/e = 206$ (100%, M^+), 191 (63.3%, $M^+ - CH_3$), 187 (10.0%, $M^+ - F$), 178 (6.0%, $M^+ - C_2H_5$), 177 (9.0%, $M^+ - C_2H_5$), 171 (23.3%, $M^+ - CH_3 - HF$), 159 (8.0%, $M^+ - SCH_3$), 158 (35.0%, $M^+ - C_2H_5 - HF$), 157 (16.6%, $M^+ - C_2H_5 - HF$), 145 (3.3%, $M^+ - SC_2H_5$), 69 (13.3%, CF_3^+), 45 (83.3%, CHS^+), 29 (56.6%, $C_2H_5^+$).

4. EI-MS: $m/e = 206$ (100%, M^+), 191 (53.3%, $M^+ - CH_3$), 189 (6.6%, $M^+ - CH_3 - H_2$), 187 (6.5%, $M^+ - F$), 185 (3.2%, $M^+ - HF - H$), 173 (6.6%, $M^+ - SH$), 171 (26.6%, $M^+ - CH_3 - HF$), 159 (23.3%, $M^+ - SCH_3$), 127 (10.0%, $C_6H_4FS^+$), 109 (7.0%, $C_6H_5S^+$), 91 (3.3%, $C_3H_7^+$), 45 (33.3%, CHS^+).

5. EI-MS: $m/e = 206$ (100%, M^+), 191 (9.7%, $M^+ - CH_3$), 187 (4.8%, $M^+ - F$), 185 (3.2%, $M^+ - HF - H$), 173 (32.2%, $M^+ - SH$), 171 (8.0%, $M^+ - CH_3$

–HF), 159 (11.2%, $M^+ - SCH_3$), 137 (6.4%, $M^+ - CF_3$), 127 (8.0%, $C_6H_4FS^+$), 109 (6.2%, $C_6H_5S^+$), 91 (12.9%, $C_2H_7^+$), 45 (24.1%, CHS^+).

6. EI-MS: $m/e = 220$ (100%, M^+), 205 (68.0%, $M^+ - CH_3$), 201 (3.2%, $M^+ - F$), 192 (29.0%, $M^+ - C_2H_4$), 191 (32.2%, $M^+ - C_2H_5$), 185 (9.6%, $M^+ - CH_3 - HF$), 172 (6.4%, $M^+ - C_2H_4 - HF$), 171 (16.1%, $M^+ - CH_3 - H_2S$), 159 (35.4%, $M^+ - SC_2H_5$), 127 (8.0%, $C_6H_4FS^+$), 69 (3.2%, CF_3^+), 45 (29.0%, CHS^+), 29 (12.9%, $C_2H_5^+$).

7. EI-MS: $m/e = 220$ (100%, M^+), 205 (51.6%, $M^+ - CH_3$), 201 (4.8%, $M^+ - F$), 192 (41.9%, $M^+ - C_2H_4$), 191 (6.4%, $M^+ - C_2H_5$), 185 (16.2%, $M^+ - CH_3 - HF$), 172 (6.4%, $M^+ - C_2H_4 - HF$), 171 (4.8%, $M^+ - CH_3 - H_2S$), 159 (41.9%, $M^+ - SC_2H_5$), 127 (8.0%, $C_6H_4FS^+$), 123 (4.8%, $C_7H_5S^+$), 69 (3.2%, CF_3^+), 45 (25.8%, CHS^+), 29 (12.9%, $C_2H_5^+$).

3.4.2. Method B

The same procedure described above was followed using *sec*-butyllithium in cyclohexane at -50°C as metallating agent.

When 2.7 mmol of organolithium were used, only the starting material was recovered.

When 5.4 mmol of organolithium were used, the reaction mixture was formed by 3 (80%) and traces of 4, 5, 6, 7.

When 10.8 mmol of organolithium were used, 3, 6, 7 were detected in the ratio of 10:48:40 respectively.

3.4.3. Method C

A solution of butyllithium in hexane (2.7 mmol), was cooled to -70°C under argon and a solution of 1a (2.5 mmol) in hexane (10 ml) was added. Finely powdered potassium *tert*-butoxide (2.7 mmol) was added. After 6 h, an excess of iodomethane (3 mmol) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water and worked up as described above. The GC/MS analyses, see Table 1, showed the starting material (90%), 3 (8%) and 4 (2%).

When 5.4 mmol of superbase were used, the reaction mixture showed the presence of the starting material (10%) and the products 3 and 4 in the ratio of 75:15 respectively.

When 10.8 mmol of superbase were used, the reaction mixture showed four products (3, 4, 6, 7) in the ratio of 6:16:47:31 respectively.

3.4.4. Reaction of monometallated 1a with carbon dioxide: [4-(trifluoromethyl)phenylthio]acetic acid (17)

The monometallated mixture of 1a, obtained as described above (Method B, Section 3.4.2) by reaction with 2 molar equivalents of *sec*-butyllithium, was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated with 10% aqueous sodium bicarbonate and then with diethyl ether. The alkali layer

was separated, washed with diethyl ether, and then acidified with cold concentrated hydrochloric acid, extracted with diethyl ether, dried (Na_2SO_4) and evaporated. The crude product was crystallized from (1:1) aqueous ethanol. Yield 68%; m.p. $108-110^\circ\text{C}$: IR (nujol): 3450 (OH), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ : 3.80 (s, 2H, SCH_2), 7.56 (d, 2H, Ar-H), 7.65 (d, 2H, Ar-H), 9.22 (s, 1H, CO_2H , D_2O exchanged); ^{13}C { ^1H } NMR ($CDCl_3$) δ : 35.15 (t, SCH_2), 124.02 (q, CF_3 , $^1J_{CF} = 278.55\text{ Hz}$), 125.88 (dm, C-3 and C-5, $^3J_{CF} = 3.67\text{ Hz}$), 128.02 (d, C-2 and C-6), 128.07 (qm, C-4, $^2J_{CF} = 32.5\text{ Hz}$), 139.95 (s, C-1), 175.10 (s, CO_2H). EI-MS: $m/e = 236$ (100%, M^+), 219 (4.0%, $M^+ - OH$), 218 (3.4%, $M^+ - H_2O$), 217 (8.8%, $M^+ - F$), 191 (93.3%, $M^+ - CO_2H$), 178 (18.3%, $M^+ - CH_2O - CO$), 177 (8.9%, $M^+ - CH_3CO_2H$), 171 (35.5%, $M^+ - CO_2 - F$), 159 (8.2%, $M^+ - CH_2O - CO - F$), 158 (12.3%, $M^+ - CH_2O - CO - HF$), 157 (11.5%, $M^+ - CH_3CO_2H - HF$), 145 (8.1%, $M^+ - SC_2H_5$), 127 (11.1%, $C_6H_4FS^+$), 114 (6.2%, $C_6H_4F_2^+$), 108 (6.7%, $C_6H_5S^+$), 69 (11.9%, CF_3^+), 45 (40.6%, SCH^+). Elemental analysis. Found: C, 45.70; H, 2.91; S, 13.44. $C_9H_7F_3O_2S$ (236.2) calcd.: C, 45.76; H, 2.99; S, 13.57%.

3.4.5. Reaction of bimetalated 1a with carbon dioxide: [2-carboxy-4-(trifluoromethyl)phenylthio]acetic acid (18)

The bimetalated mixture of 1a, obtained by reaction with 4 molar equivalents of butyllithium (Method A, Section 3.4.1), was poured onto ca. 100 g of crushed solid carbon dioxide. After the usual work-up, the crude product was crystallized from acetone. Yield 55%; m.p. 165°C : IR (nujol): 3390 (OH), 1700 , 1680 cm^{-1} (C=O); ^1H NMR ($DMSO-d_6$) δ : 2.51 (s, 2H, CH_2), 4.05 (s, br, 2H, OH), 7.55 (d, 1H, H-6), 7.85 (d, 1H, H-5), 8.12 (s, 1H, H-3); ^{13}C { ^1H } NMR ($DMSO-d_6$) δ : 34.23 (t, CH_2), 124.24 (qt, CF_3 , $^1J_{CF} = 267.97\text{ Hz}$), 124.91 (qm, C-5, $^3J_{CF} = 4.87\text{ Hz}$), 126.02 (m, C-6), 126.64 (d, C-3, $^3J_{CF} = 2.92\text{ Hz}$), 127.44 (m, C-4, $^2J_{CF} = 33.05\text{ Hz}$), 128.18 (m, C-1), 147.78 (s, br, C-2), 166.66 (d, Ar-CO), 160.67 (t, CH_2-CO); EI-MS: $m/e = 280$ (60.2%, M^+), 262 (27.9%, $M^+ - H_2O$), 261 (6.8%, $M^+ - F$), 236 (19.8%, $M^+ - CO_2$), 235 (30.6%, $M^+ - CO_2H$), 221 (19.1%, $M^+ - CH_2CO_2H$), 218 (63.7%, $M^+ - CO_2 - H_2O$), 217 (10.2%, $M^+ - CO_2 - F$), 205 (45.9%, $M^+ - CO - CH_2O - OH$), 189 (26.7%, $C_6H_4F_3S^+$), 171 (32.0%, $C_6H_4F_3S^+$), 157 (25.2%, $C_7H_5F_3S^+$), 69 (36.8%, CF_3^+), 45 (100%, CO_2H^+). Elemental analysis. Found: C, 42.78; H, 2.45; S, 11.30. $C_{10}H_7F_3O_4S$ (280.2) calcd.: C, 42.86; H, 2.52; S, 11.44%.

3.4.6. Reaction of bimetalated 1a with 4-methylbenzoyl chloride: 3-(4-methylphenyl)-5-(trifluoromethyl)-benzo[b]thiophene (19)

The bimetalated mixture of 1a (2.5 mmol), obtained as described above, was cooled to -80°C and treated

dropwise under argon with a solution of 4-methylbenzoyl chloride (2.6 mmol) in diethyl ether (10 ml). When the addition was complete, the mixture was stirred at -80°C for 1 h, then allowed to warm up, left at room temperature for 2 h, and poured into water. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic extracts dried (Na_2SO_4). The HPLC analysis showed the presence of four products, which were separated by flash-chromatography using hexane–ethyl acetate (9:1) as eluent. The first fraction was identified as 3-(4-methylphenyl)-5-(trifluoromethyl)benzo[b]thiophene (19). Yield 46%; m.p. 94–95°C; ^1H NMR (CDCl_3) δ : 2.48 (s, 3H, CH_3), 7.35 (d, 2H, H-12 and H-14), 7.49 (d, 2H, H-11 and H-15), 7.51 (s, 1H, H-2), 7.63 (d, 1H, H-7), 8.03 (d, 1H, H-6), 8.19 (s, 1H, H-4); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 21.26 (qt, CH_3), 120.16 (dm, C-4 or C-6, $^3J_{\text{CF}} = 4.3$ Hz), 120.63 (dm, C-4 or C-6, $^3J_{\text{CF}} = 3.0$ Hz), 123.43 (d, C-2 or C-7), 124.69 (qd, CF_3 , $^1J_{\text{CF}} = 270.67$ Hz), 124.81 (d, C-2 or C-7), 126.94 (qd, C-5, $^2J_{\text{CF}} = 32.17$ Hz), 128.51 (dd, C-11 and C-15), 129.67 (dt, C-12 and C-14), 132.16 (t, C-10), 137.70 (m, C-13), 137.88 (q, C-9), 138.43 (s, br, C-3), 143.69 (q, C-8). EI-MS: $m/e = 292$ (100%, M^+), 291 (27.8%, $\text{M}^+ - \text{H}$), 277 (2.6%, $\text{M}^+ - \text{CH}_3$), 273 (3.1%, $\text{M}^+ - \text{F}$), 271 (1.6%, $\text{M}^+ - \text{HF}$), 223 (8.2%, $\text{M}^+ - \text{CF}_3$), 222 (8.5%, $\text{M}^+ - \text{CS} - \text{CH}=\text{CH}$), 221 (14.8%, $\text{M}^+ - \text{CHS} - \text{CH}=\text{CH}$), 189 (2.9%, $\text{C}_8\text{H}_4\text{F}_3\text{S}^+$), 136 (6.4%, $\text{C}_8\text{H}_8\text{S}^+$), 135 (5.6%, $\text{C}_8\text{H}_7\text{S}^+$), 69 (16.2%, CF_3^+). Elemental analysis. Found: C, 65.68; H, 3.85; S, 10.83. $\text{C}_{16}\text{H}_{11}\text{F}_3\text{S}$ (292.3) calcd.: C, 65.74; H, 3.79; S, 10.97%.

The second fraction was 4-methyl benzoic acid 1-(4-methylphenyl)-2-[(4-trifluoromethyl)phenylthio]ethyl ester (20). Yield 19%; m.p. 128–130°C; IR (nujol): 1732 cm^{-1} (C=O); ^1H NMR (CDCl_3) δ : 2.33 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.62 (s, 1H, H-2), 7.14 (d, 2H, H-12 and H-14 or H-18 and H-20 or H-21 and H-17), 7.29 (d, 2H, H-12 and H-14 or H-18 and H-20 or H-21 and H-17), 7.38 (d, 2H, H-12 and H-14 or H-18 and H-20 or H-21 and H-17), 7.49 (dd, 4H, H-4, H-5, H-7 and H-8), 8.88 (d, 2H, H-11 and H-15); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 21.79 (qt, CH_3), 21.88 (qt, CH_3), 109.26 (d, C-2), 124.03 (qd, CF_3 , $^1J_{\text{CF}} = 275$ Hz), 124.46 (dd, C-17 and C-21), 125.87 (dm, C-5 and C-7, $^3J_{\text{CF}} = 3.67$ Hz), 125.98 (t, C-10), 128.52 (qd, C-6, $^2J_{\text{CF}} = 32.18$ Hz), 128.53 (dd, C-11 and C-15), 129.39 (dm, C-12 and C-14 or C-18 and C-20), 129.47 (dm, C-12 and C-14 or C-18 and C-20), 130.38 (dd, C-4 and C-8), 130.93 (t, C-16), 139.23 (m, C-19), 140.62 (m, C-3), 144.76 (m, C-13), 149.39 (m, C-1), 163.76 (s, broad, C-9). EI-MS: $m/e = 428$ (41%, M^+), 281 (2.4%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2 - \text{H}$), 251 (15.8%, $\text{M}^+ - \text{CF}_3\text{C}_6\text{H}_4\text{S}$), 148 (1.6%, $\text{C}_8\text{H}_8\text{O}_2^+$), 119 (100%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$), 91 (30.3%, C_7H_7^+), 65 (13.2%, C_7H_5^+). Elemental analysis. Found: C, 67.16; H, 4.54; S, 7.35. $\text{C}_{24}\text{H}_{19}\text{F}_3\text{O}_3\text{S}$ (428.5) calcd.: C, 67.28; H, 4.47; S, 7.48%.

The third fraction was 4-methyl benzoic acid 1,3-bis-(4-methylphenyl)-2-[(4-trifluoromethyl)phenylthio]-3-oxo-1-propenyl ester (21). Yield 15%; m.p. 150–152°C; IR (nujol): 1729 and 1656 cm^{-1} (C=O); ^1H NMR (CDCl_3) δ : 2.34 (s, 9H, CH_3), 7.11 (d, 2H, H-18 and H-22 or H-19 and H-21), 7.17 (d, 4H, H-13, H-15, H-18 and H-22 or H-13, H-15, H-19 and H-21), 7.47 (dd, 4H, H-24, H-25, H-27 and H-28), 7.59 (d, 2H, H-6 and H-8), 7.71 (d, 2H, H-5 and H-9), 7.77 (d, 2H, H-12 and H-16); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 21.52 (qt, CH_3), 21.72 (qt, two CH_3), 118.69 (s, C-2), 124.01 (qd, CF_3 , $^1J_{\text{CF}} = 273.15$ Hz), 125.55 (t, C-11), 125.85 (dm, C-25 and C-27, $^3J_{\text{CF}} = 3.22$ Hz), 128.42 (dd, C-18 and C-22 or C-12 and C-14), 128.47 (dd, C-18 and C-22 or C-12 and C-14), 128.54 (dm, C-26, $^2J_{\text{CF}} = 32.17$ Hz), 129.04 (dm, C-13 and C-15 or C-19 and C-21 or C-6 and C-8), 129.14 (dm, C-13 and C-15 or C-19 and C-21 or C-6 and C-8), 129.20 (dm, C-13 and C-15 or C-19 and C-21 or C-6 and C-8), 129.60 (dd, C-5 and C-9), 130.18 (dd, C-24 and C-28), 130.25 (t, C-17 or C-4), 133.04 (t, C-17 or C-4), 139.26 (t, C-23), 140.69 (m, C-20), 144.38 (m, C-14), 144.71 (m, C-7), 155.76 (s, broad, C-1), 163.91 (s, broad, C-10), 191.05 (s, broad, C-3). EI-MS: $m/e = 546$ (15.5%, M^+), 527 (0.4%, $\text{M}^+ - \text{F}$), 411 (0.5%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2$), 369 (14.1%, $\text{M}^+ - \text{CF}_3\text{C}_6\text{H}_4\text{S}$), 307 (0.4%, $\text{M}^+ - (\text{CH}_3\text{C}_6\text{H}_4\text{CO})_2 - \text{F}$), 292 (0.1%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{C}=\text{CSC}_6\text{H}_4\text{CF}_3$), 119 (100%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$), 91 (21.8%, C_7H_7^+), 65 (6.0%, C_7H_5^+); CI-MS: $m/e = 547$ (3.1%, $\text{M}^+ \text{H}$), 546 (4.7%, M^+), 527 (13.8%, $\text{M}^+ - \text{F}$), 411 (12.1%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2$), 391 (1.9%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2 - \text{HF}$), 369 (41.9%, $\text{M}^+ - \text{CF}_3\text{C}_6\text{H}_4\text{S}$), 137 (3.6%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}_2\text{H}^+$), 119 (100%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$), 91 (2.8%, C_7H_7^+). Elemental analysis. Found: C, 70.20; H, 4.55; S, 5.98. $\text{C}_{32}\text{H}_{25}\text{F}_3\text{O}_3\text{S}$ (546.6) calcd.: C, 70.32; H, 4.61; S, 5.87%.

The fourth fraction was formed by a small amount (ca. 5%) of 4-methyl benzoic acid 1-(4-methylphenyl)-1-[(4-(trifluoromethyl)phenylthio)methyl]-2-[4-(trifluoromethyl)phenylthio]ethyl ester (22). EI-MS: $m/e = 601$ (0.1%, $\text{M}^+ - \text{F}$), 485 (3.4%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2$), 484 (8.9%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2\text{H}$), 429 (0.9%, $\text{M}^+ - \text{CF}_3\text{C}_6\text{H}_4\text{SCH}_3$), 307 (29.5%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2\text{H} - \text{CF}_3\text{C}_6\text{H}_4\text{S}$), 159 (22.8%, $\text{C}_8\text{H}_8\text{F}_3^+$), 119 (100%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$), 91 (35.26%, C_7H_7^+), 65 (12.6%, C_7H_5^+). The structure of this compound was determined by comparison with the product 28 (see below).

3.5. Metallation of 2a

The same procedure described above (Method A, Section 3.4.1) was followed. When 1 molar equivalent of butyllithium was used the GC/MS analysis showed (see Table 1) only the starting material. With 2 molar equivalents of the same organometallic, the reaction mixture showed, besides the starting material (21%), the

products **8**, **9** in the ratio of 64:15. The same two products **8** and **9** in a 32:58 ratio were obtained performing the reaction with 3 molar equivalents of organolithium. When 4 molar equivalents of butyllithium were used the reaction mixture showed, besides **8** and **9**, the presence of **10**. The products **8**, **9**, **10** were detected in the ratio of 19:46:30 respectively. The starting material was 5%.

When 1 molar equivalent of *sec*-butyllithium was used (see Table 1), only the starting material was recovered. With 2 molar equivalents of the same organolithium, only **8** was detected; with 4 molar equivalents of organolithium **8**, **9**, **10** were detected in the ratio of 11:45:43.

When 1 molar equivalent of superbases was used, the GC/MS analyses showed the starting material (90%) besides minor amounts (10%) of **8**. With 2 molar equivalents of the same reagent, the reaction mixture, see Table 1, showed **8** (90%), the starting material (8%) and traces of **9** and **10**. With 4 molar equivalents of superbases, the reaction mixture showed **8**, **9**, **10** in the ratio of 84:6:5 respectively, and 5% of the starting material.

8. EI-MS: $m/e = 206$ (100%, M^+), 191 (46.6%, $M^+ - CH_3$), 178 (11.6%, $M^+ - C_2H_5$), 171 (38.3%, $M^+ - CH_3 - HF$), 158 (78.3%, $M^+ - C_2H_5 - HF$), 127 (11.1%, $C_6H_4FS^+$), 114 (95.0%, $C_6H_4F_2^+$), 108 (10.0%, $C_6H_4S^+$), 95 (7.0%, $C_6H_4F^+$), 69 (13.3%, CF_3^+), 45 (41.6%, CHS^+).

9. EI-MS: $m/e = 220$ (100%, M^+), 205 (24.2%, $M^+ - CH_3$), 192 (14.2%, $M^+ - C_2H_5$), 191 (37.0%, $M^+ - C_2H_5$), 185 (18.9%, $M^+ - CH_3 - HF$), 172 (88.7%, $M^+ - C_2H_5 - HF$), 171 (64.5%, $M^+ - C_2H_5 - HF$), 159 (11.4%, $M^+ - SC_2H_5$), 128 (8.0%, $C_7H_5F_2^+$), 127 (35.4%, $C_6H_4FS^+$), 121 (11.2%, $C_7H_5S^+$), 109 (8.0%, $C_6H_5S^+$), 69 (9.6%, CF_3^+), 45 (58.0%, CHS^+).

10. EI-MS: $m/e = 220$ (100%, M^+), 205 (48.3%, $M^+ - CH_3$), 192 (14.3%, $M^+ - C_2H_5$), 191 (3.2%, $M^+ - C_2H_5$), 185 (19.3%, $M^+ - CH_3 - HF$), 172 (93.5%, $M^+ - C_2H_5 - HF$), 171 (8.0%, $M^+ - C_2H_5 - HF$), 159 (11.3%, $M^+ - SC_2H_5$), 128 (11.3%, $C_7H_5F_2^+$), 127 (22.6%, $C_6H_4FS^+$), 121 (11.3%, $C_7H_5S^+$), 69 (6.4%, CF_3^+), 45 (61.3%, CHS^+).

3.5.1. Reaction of monometallated **2a** with carbon dioxide: [2-(trifluoromethyl)phenylthio]acetic acid (**25**)

The monometallated mixture of **2a** (2.5 mmol), obtained by reaction with 2 molar equivalents of *sec*-butyllithium (Method B, Section 3.4.2), was poured onto ca. 100 g of crushed solid carbon dioxide. After the usual work-up, the crude product was crystallized from (1:1) aqueous ethanol. Yield 71%; m.p. 74–76°C; IR (nujol): 3150 (OH), 1700 cm^{-1} (C=O); 1H NMR ($CDCl_3$): δ : 3.69 (s, 2H, SC_2H_5), 6.07 (s, 1H, OH, D_2O exchanged), 7.37 (t, 1H, H-4 or H-5), 7.51 (t, 1H, H-4 or H-5), 7.62 (d, 1H, H-3 or H-6), 7.69 (d, 1H, H-3 or

H-6); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ : 36.98 (t, CH_2), 123.8 (qd, CF_3 , $^1J_{CF} = 262.5$ Hz), 127.0 (qd, C-2, $^2J_{CF} = 29.07$ Hz), 127.05 (dd, C-3, $^3J_{CF} = 2.89$ Hz), 127.41 (dd, C-4), 132.34 (dd, C-6), 132.80 (dd, C-5), 133.71 (m, C-1), 175.04 (m, COOH). EI-MS: $m/e = 236$ (72.1%, M^+), 191 (100%, $M^+ - CO_2H$), 177 (8.4%, $M^+ - CH_2CO_2H$), 171 (53.6%, $M^+ - CO_2H - HF$), 159 (6.1%, $M^+ - CO_2 - HS$), 157 (12.1%, $M^+ - CH_2CO_2H - HF$), 145 (8.1%, $M^+ - SCH_2CO_2H$), 127 (19%, $C_6H_4FS^+$), 114 (8.2%, $C_6H_4F_2^+$), 108 (10.1%, $C_6H_4S^+$), 69 (14.6%, CF_3^+), 45 (77.7%, CO_2H^+ and CHS^+). Elemental analysis. Found: C, 45.68; H, 2.93; S, 13.41. $C_9H_7F_3O_2S$ (236.2) calcd.: C, 45.76; H, 2.99; S, 13.57%.

3.5.2. Reaction of monometallated **2a** with chlorotrimethylsilane

The monometallated mixture of **2a** (2.5 mmol), obtained by reaction with 2 molar equivalents of *sec*-butyllithium (Method B, Section 3.4.2), was cooled to $-20^\circ C$ and a solution of chlorotrimethylsilane (2.7 mmol) in anhydrous diethyl ether (10 ml) was gradually added under argon. When the addition was complete the mixture was stirred at $-20^\circ C$ for 1 h, then allowed to warm up, left at room temperature for 2 h, and poured into water. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic extracts dried (Na_2SO_4). The GC/MS analysis showed two products in an 85:15 ratio, which were isolated by flash-chromatography using hexane as eluent. The first fraction was identified as trimethyl [[2-(trifluoromethyl)phenylthio]methyl]silane (**26**). Yield 73%. Oil, n_D^{20} 1.4920; 1H NMR ($CDCl_3$): δ : 0.21 (s, 9H, CH_3), 2.19 (s, 2H, CH_2), 7.19 (t, 1H, H-4), 7.47 (m, 2H, H-3 and H-5), 7.61 (d, 1H, H-6); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ : -1.68 (q, CH_3), 18.73 (t, CH_2), 124.02 (qd, CF_3 , $^1J_{CF} = 272.47$ Hz), 124.18 (dd, C-4), 126.43 (dm, C-3, $^3J_{CF} = 5.47$ Hz), 127.07 (dd, C-6), 127.54 (qd, C-2, $^2J_{CF} = 30.37$ Hz), 131.77 (dd, C-5), 140.43 (t, broad, C-1); EI-MS: $m/e = 264$ (9.7%, M^+), 249 (3.2%, $M^+ - CH_3$), 172 (43.5%, $M^+ - FSi(CH_3)_3$), 153 (20.9%, $M^+ - FSi(CH_3)_3 - F$), 152 (41.9%, $M^+ - FSi(CH_3)_3 - HF$), 127 (19.3%, $C_6H_4FS^+$), 109 (8.1%, $C_6H_4S^+$), 77 (33.8%, $C_6H_5^+$), 73 (100%, $Si(CH_3)_3^+$), 69 (9.8%, CF_3^+), 45 (50.0%, CHS^+). Elemental analysis. Found: C, 49.89; H, 5.67; S, 12.01. $C_{11}H_{15}F_3SSi$ (264.4) calcd.: C, 49.97; H, 5.72; S, 12.13%.

The second fraction was identified as **32** (see below). Yield 10%.

3.5.3. Reaction of monometallated **2a** with *N*-methoxy-*N*-methyl-4-methylbenzamide: 1-[4-(methoxyphenyl)]-2-[2-(trifluoromethyl)phenylthio]-1-ethanone (**27**)

The monometallated mixture of **2a** (2.5 mmol), obtained by reaction with 2 molar equivalents of *sec*-butyllithium (Method B, Section 3.4.2), was treated at

0°C with a solution of *N*-methoxy-*N*-methyl-4-methylbenzamide (2.6 mmol) in anhydrous diethyl ether (10 ml). When the addition was complete, the mixture was stirred for 1 h at the same temperature, then poured into water and acidified with 5% hydrochloric acid. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic solutions dried (Na_2SO_4). Yield 58%. The crude product was crystallized from ethanol, m.p. 100–102°C; IR (nujol): 1689 cm^{-1} (C=O); ^1H NMR (CDCl_3) δ : 2.39 (s, 3H, CH_3), 4.26 (s, 2H, SCH_2), 7.24 (d, 2H, H-11 and H-13), 7.30 (t, 1H, H-6 or H-7), 7.43 (t, 1H, H-6 or H-7), 7.55 (d, 1H, H-5 or H-8), 7.63 (d, 1H, H-5 or H-8), 7.83 (d, 2H, H-10 and H-14); ^{13}C [^1H] NMR (CDCl_3) δ : 21.61 (qt, CH_3), 41.39 (t, CH_2), 123.59 (qd, CF_3 , $J_{\text{C-F}} = 271.87$ Hz), 126.78 (m, C-5, $J_{\text{C-F}} = 5.47$ Hz), 126.93 (dd, C-6), 128.71 (dd, C-10 and C-14), 129.36 (dm, C-11 and C-13), 130.74 (qd, C-4, $J_{\text{C-F}} = 29.77$ Hz), 132.11 (dd, C-8), 132.64 (t, C-9), 132.96 (dd, C-7), 134.30 (m, C-3), 144.61 (m, C-12), 193.21 (t, broad, CO); EI-MS: $m/e = 310$ (14.2%, M^+), 291 (0.3%, $\text{M}^+ - \text{F}$), 268 (0.4%, $\text{M}^+ - \text{CH}_3\text{CO}$), 191 (1.6%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}$), 177 (1.3%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{COCH}_2$), 171 (2.4%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO} - \text{HF}$), 157 (2.0%, $\text{C}_6\text{H}_5\text{F}_3^+$), 145 (1.3%, $\text{C}_7\text{H}_5\text{F}_3^+$), 119 (100%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$), 91 (29.9%, H^+), 65 (13.4%, C_5H_5^+). Elemental analysis. Found: C, 61.84; H, 4.15; S, 10.21. $\text{C}_{16}\text{H}_{13}\text{F}_3\text{OS}$ (310.3) calcd.: C, 61.93; H, 4.22; S, 10.33%.

When 4-methylbenzoyl chloride was used instead of amide a mixture of two products was obtained, which was flash-chromatographed using hexane–ethyl acetate (9:1) as eluent. The first fraction was 27. Yield 15%. The second fraction was 4-methyl benzoic acid 1-(4-methylphenyl)-1-[[2-(trifluoromethyl)phenylthio]methyl]-2-[2-(trifluoromethyl)phenylthio]ethyl ester (28). Yield 51%; m.p. 168–170°C. IR (nujol): 1720 cm^{-1} (C=O). ^1H NMR ($\text{DMSO}-d_6$) δ : 2.33 (s, 3H, $\text{Ar}-\text{CH}_3$), 2.44 (s, 3H, $\text{Ar}-\text{CH}_3$), 4.27 (q, 4H, SCH_2), 7.21 (d, 2H, H-25 and H-27), 7.33 (d, 2H, H-19 and H-21), 7.37 (t, 2H, H-7 and H-13 or H-8 and H-12), 7.46 (d, 2H, H-24 and H-28), 7.55 (t, 2H, H-7 and H-13 or H-8 and H-12), 7.65 (d, 4H, H-6, H-9, H-11 and H-14), 7.71 (d, 2H, H-18 and H-22); ^{13}C [^1H] NMR (CDCl_3) δ : 21.03 (qt, CH_3), 21.67 (qt, CH_3), 42.73 (t, SCH_2), 84.42 (m, C-2), 123.61 (qd, CF_3 , $J_{\text{C-F}} = 273.37$ Hz), 125.15 (dd, C-7 and C-13), 126.21 (dd, C-9 and C-11), 126.45 (dm, C-6 and C-14, $J_{\text{C-F}} = 5.47$ Hz), 127.39 (m, C-17), 128.81 (dd, C-19 and C-21), 129.10 (dt, C-25 and C-27), 129.74 (dt, C-24 and C-28), 130.47 (qd, C-5 and C-15, $J_{\text{C-F}} = 29.77$ Hz), 131.84 (dd, C-18 and C-22), 132.99 (dd, C-8 and C-12), 135.12 (m, C-26), 137.52 (m, C-4 and C-10), 137.72 (m, C-23), 143.69 (m, C-20), 164.75 (t, CO). EI-MS: $m/e = 307$ (63.4%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2 - \text{CF}_3\text{C}_6\text{H}_4\text{SH}$), 191 (5.7%, $\text{CF}_3\text{C}_6\text{H}_4\text{SCH}_2^+$), 178 (2.6%, $\text{CF}_3\text{C}_6\text{H}_4\text{SH}^+$), 159

(40.8%, $\text{CH}_3\text{C}_6\text{H}_4\text{SCH}_2^+$), 119 (100%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$), 105 (11.9%, $\text{C}_6\text{H}_5\text{CO}^+$), 91 (34.1%, C_7H_7^+), 65 (9.3%, C_5H_5^+), 45 (8.4%, CHS^+); CI-MS: $m/e = 485$ (16.2%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2$), 484 (8.6%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2\text{H}$), 465 (2.8%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2 - \text{HF}$), 443 (3.2%, $\text{M}^+ - \text{CF}_3\text{C}_6\text{H}_4\text{S}$), 423 (8.3%, $\text{M}^+ - \text{CF}_3\text{C}_6\text{H}_4\text{S} - \text{HF}$), 393 (1%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2 - \text{C}_6\text{H}_5\text{CH}_2$), 307 (100%, $\text{M}^+ - \text{CH}_3\text{C}_6\text{H}_4\text{CO}_2 - \text{CF}_3\text{C}_6\text{H}_4\text{SH}$), 191 (6.1%, $\text{CF}_3\text{C}_6\text{H}_4\text{SCH}_2^+$), 178 (3.8%, $\text{CF}_3\text{C}_6\text{H}_4\text{SH}^+$), 159 (1.9%, $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2^+$), 119 (45.6%, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$), 105 (6.9%, $\text{C}_6\text{H}_5\text{CO}^+$), 91 (4.9%, C_5H_5^+); ions ($\text{M}^+ - \text{H}$) and ($\text{M}^+ - \text{F}$) are recorded in scan acquisition mode (mass range 400–650). Elemental analysis. Found: C, 61.84; H, 4.16; S, 10.42. $\text{C}_{32}\text{H}_{26}\text{F}_6\text{O}_2\text{S}_2$ (620.7) calcd.: C, 61.93; H, 4.22; S, 10.33%.

3.5.4. Reaction of bimetalated 2a with 4-methylbenzoyl chloride

The bimetalated mixture of 2a (2.5 mmol), obtained by reaction with 4 molar equivalents of butyllithium (Method A, Section 3.4.1), was treated at -80°C with a solution of 4-methylbenzoyl chloride (2.6 mmol) in diethyl ether (10 ml). The HPLC analysis of the reaction mixture showed two products in a 65:35 ratio, which were isolated by flash-chromatography using hexane–ethyl acetate (9:1) as eluent. The first compound was identified as 3-(4-methylphenyl)-7-(trifluoromethyl)benzo[b]thiophene (29). Yield 55%; crystallized from petroleum ether (b.p. $40\text{--}70^\circ\text{C}$), m.p. $74\text{--}75^\circ\text{C}$; ^1H NMR (CDCl_3) δ : 2.47 (s, 3H, CH_3), 7.34 (d, 2H, H-12 and H-14), 7.49 (m, 4H, H-2, H-5, H-11, H-15), 7.72 (d, 1H, H-4), 8.08 (d, 1H, H-6); ^{13}C [^1H] NMR (CDCl_3) δ : 21.25 (qt, CH_3), 122.22 (m, C-6, $J_{\text{C-F}} = 4.2$ Hz), 124.05 (d, C-2), 124.13 (qd, CF_3 , $J_{\text{C-F}} = 276.75$ Hz), 124.35 (dd, br, C-5), 125.15 (qm, C-7, $J_{\text{C-F}} = 32.7$ Hz), 126.54 (dd, C-4), 128.65 (dd, C-11 and C-15), 129.54 (dm, C-12 and C-14), 132.34 (dt, C-10), 136.91 (m, C-9), 137.76 (q, C-13), 137.91 (s, br, C-3), 139.75 (t, C-8). EI-MS: $m/e = 292$ (100%, M^+), 291 (24.6%, $\text{M}^+ - \text{H}$), 277 (2.0%, $\text{M}^+ - \text{CH}_3$), 273 (2.3%, $\text{M}^+ - \text{F}$), 271 (2.9%, $\text{M}^+ - \text{H} - \text{HF}$), 247 (2.1%, $\text{M}^+ - \text{CHS}$), 223 (6.7%, $\text{M}^+ - \text{CF}_3$), 222 (6.7%, $\text{M}^+ - \text{CS} - \text{CH}=\text{CH}$), 221 (10.1%, $\text{M}^+ - \text{CSH} - \text{CH}=\text{CH}$), 189 (1.8%, $\text{C}_8\text{H}_5\text{F}_3\text{S}^+$), 136 (2.6%, $\text{C}_8\text{H}_5\text{S}^+$), 135 (4.3%, $\text{C}_8\text{H}_7\text{S}^+$), 69 (3.0%, CF_3^+), 45 (3.6%, CHS^+). Elemental analysis. Found: C, 65.65; H, 3.74; S, 10.88. $\text{C}_{16}\text{H}_{11}\text{F}_3\text{S}$ (292.3) calcd.: C, 61.74; H, 3.79; S, 10.97%.

The second fraction was 28. Yield 23%.

3.5.5. Reaction of bimetalated 2a with carbon dioxide

After carbonation of the bimetalated 2a (2.5 mmol) two compounds were obtained. The first one was isolated from the ethereal solution and was identified as 25 (yield 15%), the second, ether insoluble, was filtered and identified as 2,4-dicarboxy-3-fluorobenzo-

[b]thiophene (**30**). Yield 44%; crystallized from ethanol, m.p. 270 °C (decomp.); IR (nujol): 3410 (OH), 1690, 1670 cm^{-1} (C=O); ^1H NMR (DMSO- d_6) δ : 4.30 (s, 1H, OH, D_2O exchanged), 7.63 (t, 1H, H-6), 7.75 (d, 1H, H-7), 8.19 (d, 1H, H-5); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 115.02 (d, C-9, $^2J_{\text{CF}} = 9.97$ Hz), 124.99 (d, C-2, $^2J_{\text{CF}} = 19.42$ Hz), 126.54 (dd, C-5 or C-6 or C-7), 126.61 (d, C-5 or C-6 or C-7), 127.93 (d, C-5 or C-6 or C-7), 129.69 (m, C-4, $^3J_{\text{CF}} = 4.2$ Hz), 137.32 (t, C-8, $^3J_{\text{CF}} = 7.27$ Hz), 152.38 (d, C-3, $^1J_{\text{CF}} = 281.55$ Hz) 161.91 (d, CO of C-2), 167.84 (d, CO of C-4); EI-MS: $m/e = 240$ (100%, M^+), 223 (37.9%, $\text{M}^+ - \text{OH}$), 222 (33.4%, $\text{M}^+ - \text{H}_2\text{O}$), 205 (10.9%, $\text{M}^+ - \text{H}_2\text{O} - \text{OH}$), 203 (7.3%, $\text{M}^+ - \text{H}_2\text{O} - \text{F}$), 196 (37.6%, $\text{M}^+ - \text{CO}_2$), 195 (15.0%, $\text{M}^+ - \text{CO}_2\text{H}$), 179 (23.3%, $\text{M}^+ - \text{CO}_2 - \text{OH}$), 178 (14.7%, $\text{M}^+ - \text{CO}_2 - \text{H}_2\text{O}$), 176 (17.8%, $\text{M}^+ - \text{CO}_2 - \text{CO}_2\text{H}$), 148 (13.1%, $\text{M}^+ - \text{CO}_2 - \text{HF} - \text{CO}$), 139 (9.0%, $\text{C}_7\text{H}_4\text{FS}^+$), 107 (23.5%, $\text{C}_6\text{H}_3\text{S}^+$), 69 (11.6%, CF_3^+), 45 (11.4%, CO_2H^+), 44 (20.3%, CO_2^+). Elemental analysis. Found: C, 49.88; H, 2.07; S, 13.28. $\text{C}_{10}\text{H}_3\text{FO}_4\text{S}$ (240.2) calcd.: C, 50.00; H, 2.10; S, 13.35%.

The same results were obtained using *sec*-butyllithium as metallating agent.

3.5.6. Reaction of bimetallated **2a** with chlorotrimethylsilane

The bimetallated mixture of **2a** (2.5 mmol), obtained by reaction with 4 molar equivalent of butyllithium (Method A, Section 3.4.1), was treated at -20°C with chlorotrimethylsilane (2.7 mmol). The GC/MS analysis of the reaction mixture showed three products in a 17:61:22 ratio. The first was identified as **26** comparing its mass spectrum with that of an authentic sample. The compounds were isolated by flash-chromatography using petroleum ether (b.p. $40\text{--}70^\circ\text{C}$)–ethyl ether (1:2) as eluent.

The first fraction was **26**. Yield 11%.

The second fraction was $\{[2\text{-(trifluoromethyl)phenylthio]methylene}\}$ -bis(trimethylsilane) (**32**). Yield 54%. Oil, n_D^{25} 1.5021; ^1H NMR (CDCl_3) δ : 0.20 (s, 18H, SiCH_3), 1.81 (s, 1H, C-H), 7.22 (m, 1H, Ar-H), 7.50 (d, br, 2H, Ar-H), 7.66 (d, 1H, Ar-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : -0.22 (q, CH_3), 18.83 (d, CH), 123.93 (qd, CF_3 , $^1J_{\text{C-F}} = 271.87$ Hz), 124.06 (dd, C-4), 126.62 (dm, C-3, $^2J_{\text{C-F}} = 5.47$ Hz), 127.94 (dd, C-6), 127.99 (qm, C-2, $^2J_{\text{C-F}} = 29.77$ Hz), 131.44 (dd, br, C-5), 140.63 (d, br, C-1); EI-MS: $m/e = 336$ (4.9%, M^+), 267 (0.3%, $\text{M}^+ - \text{CF}_3$), 152 (100%, $\text{M}^+ - 2\text{FSi}(\text{CH}_3)_3$), 139 (6.1%, $\text{C}_7\text{H}_4\text{FS}^+$), 77 (41.0%, C_6H_3^+), 73 (92.1%, $\text{Si}(\text{CH}_3)_3^+$), 69 (2.3%, CF_3^+), 45 (31.8%, CSH^+). Elemental analysis. Found: C, 49.88; H, 6.84; S, 9.41. $\text{C}_{14}\text{H}_{23}\text{F}_3\text{SSi}_2$ (336.6) calcd.: C, 49.96; H, 6.89; S, 9.53%. **32** was also obtained by metallation of **26** (3 mmol) in diethyl ether (20 ml) with a 1.2 M solution of butyllithium in hexane (3 mmol) at -10°C ,

and treating the resulting mixture with chlorotrimethylsilane (3 mmol). Yield 89%.

The third fraction was trimethyl $\{[2\text{-(trifluoromethyl)-3-(trimethylsilyl)phenylthio]methyl}\}$ silane (**31**). Yield 17%. Oil, n_D^{25} 1.4871; ^1H NMR (CDCl_3) δ : 0.27 (s, 9H, CH_3SiCH_3), 0.41 (q, 9H, ArSiCH_3), 2.25 (s, 2H, C_2H_2), 7.50 (m, 2H, H-4 and H-5), 7.63 (d, H-6); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : -1.59 (q, CH_2SiCH_3), 0.92 (qm, ArSiCH_3), 19.84 (tm, CH_2), 125.22 (q, CF_3 , $^1J_{\text{CF}} = 274.35$ Hz), 128.66 (dq, C-4), 130.33 (d, C-6), 131.77 (dd, C-5), 132.12 (qt, C-2, $^2J_{\text{CF}} = 29.77$ Hz), 139.81 (m, C-3, $^3J_{\text{CF}} = 3.0$ Hz), 141.58 (d, br, C-1); EI-MS: $m/e = 336$ (6.6%, M^+), 152 (1.9%, $\text{M}^+ - 2\text{FSi}(\text{CH}_3)_3$), 148 (3.3%, $\text{C}_9\text{H}_{12}\text{Si}^+$), 133 (3.2%, $\text{C}_8\text{H}_9\text{Si}^+$), 119 (5.3%, $\text{C}_8\text{H}_4\text{F}^+$), 89 (17.7%, C_2H_3^+), 77 (100%, C_6H_3^+), 73 (67.7%, $\text{Si}(\text{CH}_3)_3^+$), 59 (9.8%, $\text{HSi}(\text{CH}_3)_2^+$), 45 (28.3%, CH_3S^+). Elemental analysis. Found: C, 49.91; H, 6.83; S, 9.38. $\text{C}_{14}\text{H}_{23}\text{F}_3\text{SSi}_2$ (336.6) calcd.: C, 49.96; H, 6.89; S, 9.53%.

3.6. Metallation of **1b**

The same procedure described above was followed. When 1 molar equivalent of butyllithium was used the GC/MS analyses showed (see Table 1) the starting material and traces of **11** and **12**. With 2 molar equivalents of the same organometallic, the reaction mixture showed, besides a minor amount of the starting material (6%), the products **11**, **12** in the ratio of 83:11. The same two products (**11**, **12**) were obtained performing the reaction with 4 or with 8 molar equivalents of organolithium. In the first case the products ratio is 84:15, in the second 86:13.

When 1 molar equivalent of *sec*-butyllithium was used (see Table 1), only the starting material was recovered. With 2 molar equivalents of the same organolithium, besides minor amounts of the starting material (14%), **11** and **12** were detected in the ratio of 46:40; with 4 molar equivalents of organolithium **11** and **12** were detected in the ratio of 49:41.

When 1 molar equivalent of superbases was used, the GC/MS analyses showed only the starting material. With 2 molar equivalents of superbases, the reaction mixture, see Table 1, showed two products, **11** and **12**, in the ratio of 45:45 respectively, and minor amounts of the starting material (10%). With 4 molar equivalents of superbases, the reaction mixture showed three products (**11**, **12**, **13**) in the ratio of 40:40:20 respectively. With 8 molar equivalents, the reaction mixture showed the same **11**, **12**, **13** in the ratio of 41:37:22 respectively.

11. EI-MS: $m/e = 234$ (58.0%, M^+), 219 (3.3%, $\text{M}^+ - \text{CH}_3$), 215 (3.2%, $\text{M}^+ - \text{F}$), 192 (100%, $\text{M}^+ - \text{C}_3\text{H}_6$), 172 (8.3%, $\text{M}^+ - \text{C}_3\text{H}_6 - \text{HF}$), 171 (8.0%, $\text{M}^+ - \text{C}_3\text{H}_7 - \text{HF}$), 159 (48.4%, $\text{M}^+ - \text{Se}_2\text{H}_7$), 127 (6.6%, $\text{C}_6\text{H}_4\text{FS}^+$), 109 (3.3%, $\text{C}_6\text{H}_5\text{S}^+$), 69 (3.0%, CF_3^+), 43 (54.0%, C_3H_7^+).

12. EI-MS: $m/e = 234$ (51.6%, M^+), 219 (3.4%, $M^+ - CH_3$), 215 (3.1%, $M^+ - F$), 192 (100%, $M^+ - C_3H_6$), 172 (4.5%, $M^+ - C_3H_6 - HF$), 171 (4.1%, $M^+ - C_3H_7 - HF$), 159 (35.4%, $M^+ - Se_3H_7$), 127 (5.3%, $C_6H_4FS^+$), 109 (2.1%, $C_6H_5S^+$), 69 (1.2%, CF_3^+), 43 (64.5%, $C_3H_7^+$).

13. EI-MS: $m/e = 248$ (26.3%, M^+), 206 (55.2%, $M^+ - C_3H_6$), 173 (31.5%, $M^+ - SC_3H_7$), 143 (84.2%, $M^+ - C_3H_6 - CS - F$), 69 (37.5%, CF_3^+), 43 (100%, $C_3H_7^+$).

3.6.1. Reaction of metallated **1b** with carbon dioxide: 2-[(1-methylethyl)thio]-5-(trifluoromethyl)benzoic acid (23)

The metallated mixture of **1b**, obtained by reaction with 4 molar equivalents of butyllithium as described above, was poured onto ca. 100 g of crushed solid carbon dioxide. After the usual work-up, the crude product was crystallized from light petroleum. Yield 62%; m.p. 132–133 °C; IR (nujol): 3400 (OH), 1705 cm^{-1} (C=O); 1H NMR ($CDCl_3$) δ : 1.45 (d, 6H, CH_3), 3.66 (m, 1H, CH), 7.65 (m, 2H, H-3 and H-4), 8.41 (m, 1H, H-6), 9.69 (s, br, 1H, OH, D_2O exchanged); ^{13}C { 1H } NMR ($CDCl_3$) δ : 22.39 (qm, CH_3), 35.27 (dm, CH), 123.83 (qm, CF_3), $^1J_{CF} = 270.07$ Hz), 126.09 (qd, C-5, $^2J_{CF} = 33.38$ Hz), 126.66 (d, C-3), 126.71 (d, C-1), 129.08 (dm, C-6, $^3J_{C-F} = 3.6$ Hz), 129.44 (dm, C-4, $^3J_{C-F} = 4.2$ Hz), 148.51 (t, C-2), 170.1 (d, CO_2H). EI-MS: $m/e = 264$ (16.4%, M^+), 231 (4.9%, $M^+ - SH$), 222 (29.0%, $M^+ - C_3H_6$), 204 (100%, $M^+ - C_3H_6 - H_2O$), 176 (9.0%, $M^+ - C_3H_6 - H_2O - CO$), 157 (8.1%, $M^+ - C_3H_6 - H_2O - CO - F$), 156 (8.2%, $M^+ - C_3H_6 - H_2O - CO - HF$), 43 (57.3%, $C_3H_7^+$). Elemental analysis. Found: C, 49.88; H, 4.15; S, 12.01. $C_{11}H_{11}F_3O_2S$ (264.3) calcd.: C, 50.00; H, 4.20; S, 12.13%.

3.7. Metallation of **2b**

The same procedure described above was followed. When 1 molar equivalent of butyllithium was used the GC/MS analyses showed (see Table 1) only the starting material. With 2 molar equivalents of the same organometallic, the reaction mixture showed, besides a minor amount of the starting material (4%), the product **14** (96%). Similar results were obtained performing the reaction with 4 or 8 molar equivalents of organolithium.

When 1 molar equivalent of *sec*-butyllithium was used (see Table 1), only the starting material was recovered. With 2 molar equivalents of the same organolithium, besides minor amounts of the starting material (10%), **14** and **15** were detected in the ratio of 54:36; with 4 molar equivalents of organolithium **14** and **15** were detected in the ratio of 55:37.

When 1 molar equivalent of superbases was used, the GC/MS analysis showed only the starting material. With 2 molar equivalents of superbases, the reaction

mixture, see Table 1, showed three products, **14**, **15**, **16** in the ratio of 45:45:10 respectively. Similar results were obtained performing the reaction with 8 molar equivalents of the superbases mixture.

14. EI-MS: $m/e = 234$ (24.1%, M^+), 192 (37.9%, $M^+ - C_3H_6$), 172 (100%, $M^+ - C_3H_6 - HF$), 171 (23.9%, $M^+ - C_3H_7 - HF$), 127 (20.6%, $C_6H_4FS^+$), 45 (27.5%, CHS^+), 43 (50.0%, $(CH_3)_3CH^+$).

15. EI-MS: $m/e = 234$ (88.1%, M^+), 219 (3.8%, $M^+ - CH_3$), 192 (85.7%, $M^+ - C_3H_6$), 172 (100%, $M^+ - C_3H_6 - HF$), 127 (28.1%, $C_6H_4FS^+$), 71 (19.1%, $C_3H_5S^+$), 69 (10.2%, CF_3^+), 43 (95.2%, $C_3H_7^+$).

16. EI-MS: $m/e = 234$ (34.5%, M^+), 178 (75.8%, $M^+ - C_4H_8$), 158 (100%, $M^+ - C_4H_8 - HF$), 85 (22.5%, $C_3H_5S^+$), 71 (20.9%, $C_3H_5S^+$), 69 (14.5%, CF_3^+), 57 (79.5%, $C_4H_9^+$), 45 (22.3%, CHS^+).

3.7.1. Reaction of metallated **2b** with carbon dioxide: 2-[(1-methylethyl)thio]-3-(trifluoromethyl)benzoic acid (24)

The metallated mixture of **2b** (2.5 mmol), obtained by reaction with 2.4 molar equivalent of butyllithium as described above, was poured onto ca. 100 g of crushed solid carbon dioxide. After the usual work-up, the crude product was crystallized from (1:1) aqueous ethanol. Yield 73%; m.p. 98–100 °C; IR (nujol): 3100 (OH), 1680 cm^{-1} (C=O); 1H NMR ($CDCl_3$) δ : 1.27 (d, 6H, CH_3), 2.31 (s, br, 1H, OH, D_2O exchanged), 3.35 (m, 1H, CH), 7.61 (t, 1H, H-5), 7.94 (d, 1H, H-4), 8.33 (d, 1H, H-6); ^{13}C { 1H } NMR ($CDCl_3$) δ : 22.89 (qm, CH_3), 43.10 (dm, CH), 123.14 (qd, CF_3), $^1J_{CF} = 272.55$ Hz), 128.91 (d, C-5), 129.93 (dm, C-4, $^2J_{CF} = 5.47$ Hz), 131.05 (m, C-1), 133.88 (dd, C-6), 135.74 (qd, C-3, $^2J_{CF} = 29.1$ Hz), 138.68 (d, C-2), 170.46 (d, $COOH$); EI-MS: $m/e = 264$ (20.5%, M^+), 247 (1.3%, $M^+ - OH$), 246 (0.4%, $M^+ - H_2O$), 245 (0.2%, $M^+ - F$), 222 (18.0%, $M^+ - CH_3CHCH_3$), 221 (5.0%, $M^+ - CH_3CHCH_3$), 204 (100%, $M^+ - CH_3CHCH_2 - H_2O$), 185 (4.6%, $M^+ - CH_3CHCH_2 - H_2O - F$), 176 (8.3%, $M^+ - CH_3CHCH_2 - H_2O - CO$), 157 (8.6%, $C_7H_5F_3S^+$), 145 (9.8%, $C_7H_4F_3^+$), 132 (9.5%, $C_6H_3F_3^+$), 69 (8.5%, CF_3^+), 43 (31.0%, $(CH_3)_3CH^+$). Elemental analysis. Found: C, 49.92; H, 4.13; S, 12.05. $C_{11}H_{11}F_3O_2S$ (264.3) calcd.: C, 50.00; H, 4.20; S, 12.13%.

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