

# The Trifluoromethoxy Group: A Long-Range Electron-Withdrawing Substituent

Eva Castagnetti and Manfred Schlosser\*<sup>[a]</sup>

**Abstract:** Judged by its capacity to promote a hydrogen/metal permutation at an *ortho* position, the trifluoromethoxy group is superior to both the methoxy and trifluoromethyl groups. Moreover, like CF<sub>3</sub> and unlike OCH<sub>3</sub>, OCF<sub>3</sub> exerts a long-range effect that still considerably lowers the basicity of arylmetal compounds when located in a more remote *meta* or even *para* position. As a consequence, 4-(trifluoromethoxy)-

anisole is deprotonated by *sec*-butyllithium mainly, and by *tert*-butyllithium exclusively, at a position adjacent to the OCH<sub>3</sub> group rather than next to the strongly electron-withdrawing CF<sub>3</sub>O

group. 1,3-Benzodioxole undergoes *ortho* lithiation only six times faster than anisole, whereas 2,2-difluoro-1,3-benzodioxole reacts about 5000 times faster, as evidenced by competition experiments. The structure and distance dependence of substituent effects can be rationalized by assuming superposing  $\sigma$ - and  $\pi$ -polarizing interactions.

**Keywords:** hydrogen/metal exchange • intra-/intermolecular competition • isomerization • kinetics • steric hindrance • substituent effects


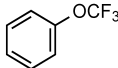

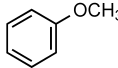
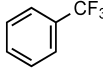

## Introduction

(Trifluoromethoxy)benzene<sup>[1]</sup> and the three bromo(trifluoromethoxy)benzene isomers<sup>[2]</sup> are readily deprotonated by *sec*-butyllithium or lithium diisopropylamide in tetrahydrofuran at  $-100^{\circ}\text{C}$  or  $-75^{\circ}\text{C}$ . This points to a marked anion-stabilizing effect. The uncommon OCF<sub>3</sub> has previously been found to acidify benzoic acids,<sup>[3–6]</sup> its electron-withdrawing power falling slightly behind that of a trifluoromethyl group, but exceeding those of both fluorine and chlorine.

## Results

We have assessed the relative rates of the hydrogen/metal interconversion process between selected benzene congeners<sup>[7–8]</sup> and *sec*-butyllithium in order to quantify the acceleration provided by the trifluoromethoxy group in comparison with other prominent substituents. The relative rates listed in Table 1 are approximate. The competition kinetic method<sup>[9–10]</sup> employed is accurate only if the reactivity of two juxtaposed substrates does not differ by much more than one power of ten, whereas, in reality, the gap between benzene and benzotrifluoride is much bigger.

Table 1. Reactivity of benzene and substituted congeners toward *sec*-butyllithium in tetrahydrofuran as probed by competition experiments. Approximate relative rates ( $k_{\text{rel}}$ ) and, after statistic correction, “factorized” rates ( $k_{\text{rel,f}}$ ).

aromatic substrate	$k_{\text{rel}}$	$k_{\text{rel,f}}$
	$1.4 \cdot 10^5$	$0.7 \cdot 10^5$
	$6.0 \cdot 10^4$	$3.0 \cdot 10^4$
	$2.4 \cdot 10^4$	$1.2 \cdot 10^4$
	$6.0 \cdot 10^3$	$3.0 \cdot 10^3$
	$1.2 \cdot 10^3$	$0.6 \cdot 10^3$
	$6.0 \cdot 10^0$	$1.0 \cdot 10^0$

A more detailed comparison was performed with anisole, (trifluoromethoxy)benzene, 1-methoxynaphthalene, 1-(trifluoromethoxy)naphthalene, 1,3-benzodioxole and 2,2-difluoro-1,3-benzodioxole as the substrates (Table 2). As with the preceding series of kinetic studies, not only the disappearance of the starting materials but also the formation of the corresponding trapping products upon consecutive carboxylation and neutralization was monitored. It proved possible to

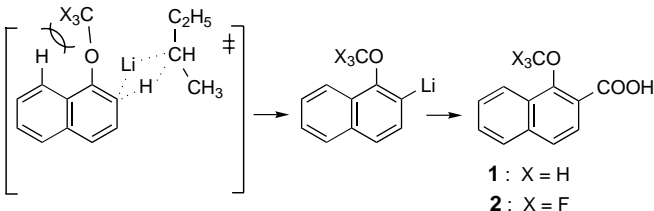
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Table 2. Competitive reactions of anisole, (trifluoromethoxy)benzene, 1-methoxynaphthalene, 1-(trifluoromethoxy)naphthalene, 1,3-benzodioxole and 2,2-difluoro-1,3-benzodioxole with *sec*-butyllithium in tetrahydrofuran: relative rates ( $k_{\text{rel}}$ ) and “factorized”, that is statistically corrected, relative rates ( $k_{\text{rel},f}$ ).

substrate	$k^{X=F}/k^{X=H}$	$k_{\text{rel}}^{X=F}$	$k_{\text{rel},f}^{X=F}$
	10	$\equiv 1.00$	$\equiv 1.00$
	30	0.45	0.90
	700	330	330

always combine compounds of similar reactivity to competing pairs, and thus to compile numerically reliable relative rates (see Table 4, below).

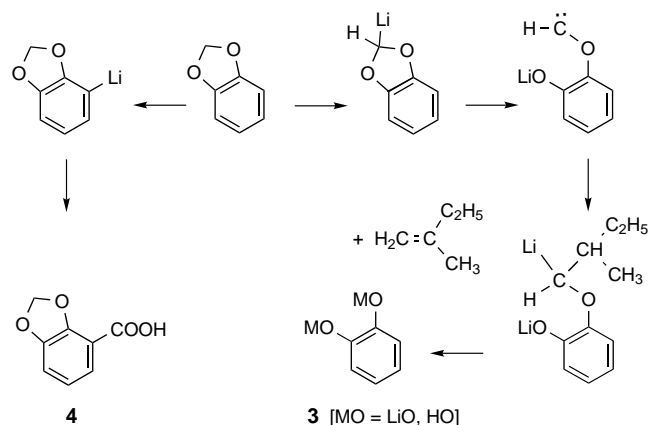
Although nearly quantitative with superbasic reagents (see Experimental Section), the metalation of 1-methoxynaphthalene (and of anisole) with *sec*-butyllithium only proceeds slowly under standard conditions. This is reflected in the poor yield (20%) of the corresponding trapping product, the carboxylic acid **1** (Scheme 1). The relative rates could nevertheless be accurately assessed. 1-(Trifluoromethoxy)naphthalene reacts smoothly with *sec*-butyllithium affording the acid **2**



Scheme 1.

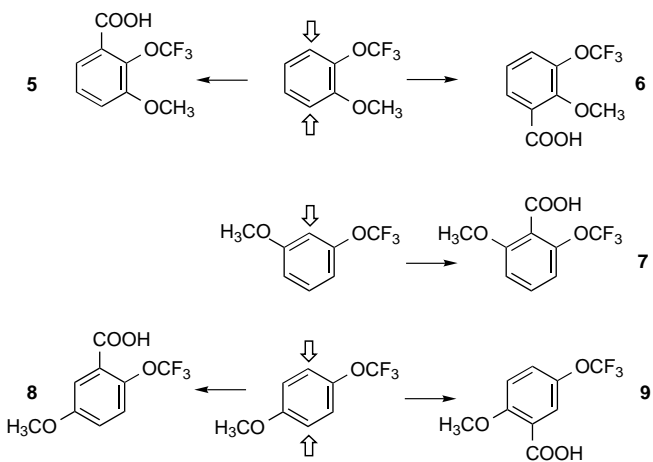
in 63% yield. Both 1-methoxynaphthalene and 1-(trifluoromethoxy)naphthalene were found to react with *sec*-butyllithium more slowly ( $k_{\text{rel},f} = 0.55$  and 0.90, respectively) than their benzene counterparts, anisole and (trifluoromethoxy)benzene. This decrease in rate was an unexpected outcome as the kinetic acidity of naphthalene considerably exceeds (4.1–9.7-fold) that of benzene.<sup>[11–13]</sup> Moreover, 1-fluoronaphthalene is known to undergo the *sec*-butyllithium promoted metalation 2.2 times (after statistical correction: 4.3 times) faster than fluorobenzene itself does.<sup>[8]</sup> We attribute the different behavior of 1-methoxynaphthalene and 1-(trifluoromethoxy)naphthalene to conformational constraints. The *peri*-hydrogen atom forces the alkoxy substituent into an almost perpendicular orientation with respect to the ring plane and prevents it from occupying a coplanar position with the carbon entity pointing away from the deprotonation site, the only position in which it could provide maximum coordinative assistance to the hydrogen/metal permutation process.

The reactivity difference observed between (trifluoromethoxy)benzene and 2,2-difluoro-1,3-benzodioxole is striking. Evidently the fluorine electron-withdrawing effect is much more efficiently transmitted to the reaction center when it can spread through two ether bridges rather than a single one. The metalation of the halogen-free 1,3-benzodioxole turned out to be slow and to lack uniformity. Large amounts of catechol (**3**, MO = HO; 1,2-dihydroxybenzene; 12%) were obtained along with the expected acid **4** (56%) even at  $-100^\circ\text{C}$  (Scheme 2). Its formation was presumably initiated by the lithiation of the acetalic methylene group and followed by a ring opening to set free an aryloxycarbene to which the *sec*-butyllithium reagent added nucleophilically before the sequence was terminated by hydride migration and olefin elimination.



Scheme 2.

So far only *intermolecular* rate comparison having been accomplished, we wondered whether the trifluoromethoxy substituent would also outperform methoxy in *intramolecular* competition reactions. To this end, 3- and 4-(trifluoromethoxy)anisole were consecutively treated with an organolithium reagent and dry ice (Scheme 3). After neutralization, a single (trifluoromethoxy)anisic acid (**7**; up to 91%) was isolated

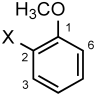
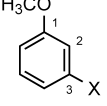
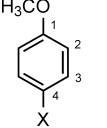


Scheme 3.

from the *meta* isomer whatever the base employed. The *para* isomer afforded the acids **8** and **9** in the ratio 1:9 with *sec*-butyllithium, and exclusively **9** (88%) with *tert*-butyllithium. The acids **5** and **6** were formed in a 1:1 ratio (79%), 10:1 ratio (78%) or 1:4 ratio (81%) when *sec*-butyllithium in the absence or presence of *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDTA) or *tert*-butyllithium were used. These regioratios confirm our rule of thumb,<sup>[14]</sup> according to which polar reagents (such as *sec*-butyllithium complexed by the tridentate donor-ligand PMDTA) favor proton abstraction from the intrinsically most acidic position, whereas noncoordinated alkylolithiums (such as *sec*- and, even more so, *tert*-butyllithium) attack preferentially or exclusively a position adjacent to the most powerful donor group.

Once more competition kinetic measurements were carried out to determine the relative rates of these reactions (Table 3). 3-(Trifluoromethoxy)anisole underwent lithiation about 3000 times faster than anisole itself, and 4-(trifluoromethoxy)anisole some 300 times faster still. Conformational reasons, as already evoked above, can explain why the trifluoromethoxy substituent accelerates the metalation of the *ortho* isomer by less than one power of ten.

Table 3. Metalation of 2-, 3- and 4-(trifluoromethoxy)anisole with *sec*-butyllithium in tetrahydrofuran: rates and “factorized” (statistically corrected) rates relative to anisole.

substrate	deprotonation site	$\frac{k^{X=OCF_3}}{k^{X=H}}$	$\frac{k_{X=OCF_3}^f}{k_{X=H}^f}$
	6-position <sup>[a]</sup>	1.7	3.3
	2-position	1500	3000
	2-position <sup>[b]</sup>	270	270

[a] 2-(Trifluoromethoxy)anisole being concomitantly metalated by *sec*-butyllithium at the 3- and 6-position (see Experimental Section), the relative rates listed in this table refer only to the organometallic attack at the site adjacent to the methoxy group. [b] 4-(Trifluoromethoxy)anisole being concomitantly metalated by *sec*-butyllithium at the 2- and 3-position (see Experimental Section), the relative rates listed in this table refer only to the organometallic attack at the site adjacent to the methoxy group.

All ether-type substrates, fluorinated or not, involved in the present investigation have been graphically arranged according to their reactivity towards *sec*-butyllithium, by using fluorobenzene as an oxygen-free reference compound (Figure 1). Whereas (trifluoromethoxy)benzene undergoes metalation 11 times more rapidly than anisole, the entire scale covers four powers of ten, going from 1-methoxynaphthalene to the 20000 times more reactive 2,2-difluoro-1,3-benzodioxole.

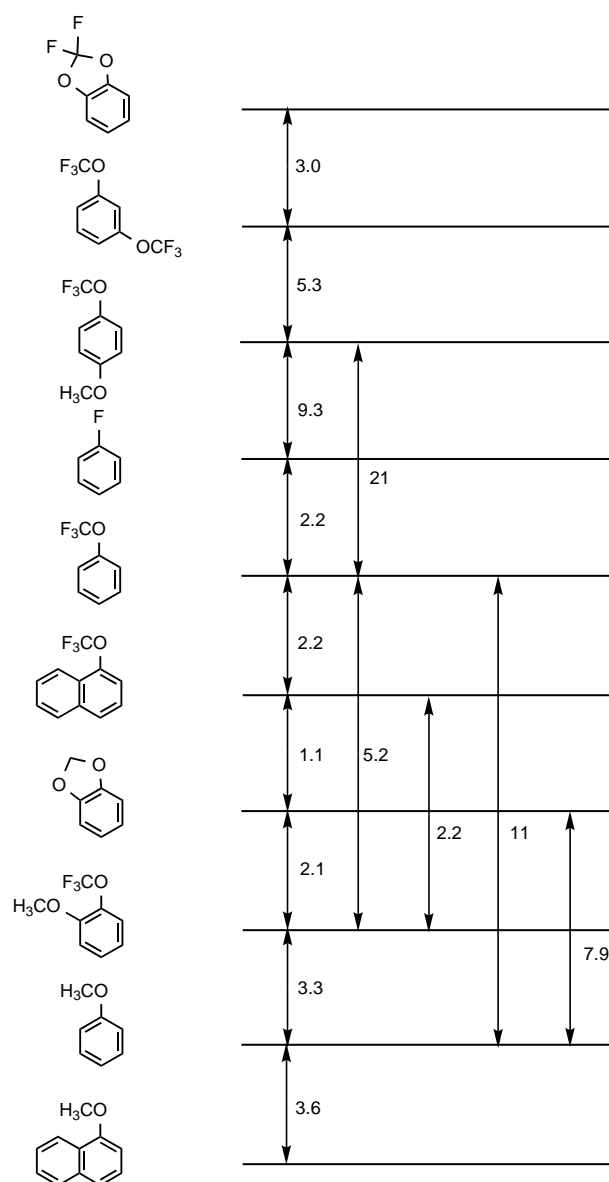


Figure 1. Graphical survey of the reactivity of anisole and congeners toward *sec*-butyllithium, the numbers representing experimentally determined relative rates without statistic correction (for further details, see Experimental Section, Table 4).

## Discussion

The data reported underscore a recent warning<sup>[15]</sup> not to assign “*ortho*-directing aptitudes” to substituents when this is merely based on regioselectivity criteria. Although trifluoromethoxy is far more powerful than methoxy as an *ortho*-metalation accelerating neighboring group, 2- and 4-(trifluoromethoxy)anisoles are preferentially deprotonated at positions adjacent to the OCH<sub>3</sub> and remote from the OCF<sub>3</sub> group. What seems to be a paradox at first sight can be well understood if one keeps in mind that the trifluoromethoxy group exerts a long range effect (see Table 3) whereas the acidity enhancement provided by a methoxy substituent is very noticeable at the *ortho* position, gets almost completely lost at the *meta*, and becomes reversed at the *para* position.<sup>[16]</sup>

When extending the scope of our survey, we identified three exemplary scenarios of how substituent effects can propagate. They may vanish abruptly with distance (as is the case with alkoxy groups), they may prove almost position-invariant (as distinctive of the trifluoromethyl group<sup>[17]</sup>), or they may (as this happens with fluorine and chlorine atoms) progressively level off by losing roughly half of their charge-stabilizing potential each time on being moved from the *ortho* to the *meta* and ultimately to the *para* position of an aryl anion.<sup>[7–8, 18–21]</sup> To rationalize this divergent behavior, we suggest that two kinds of electronic perturbations operate side by side. The electronegativity of a nitrogen, an oxygen, or a halogen atom will inevitably pull electrons in all  $\sigma$ -bonds toward the heteroelement. This  $\sigma$ -polarization diminishes, of course, with the distance from the electron-withdrawing substituent. The same substituent will simultaneously affect the  $\pi$ -electron cloud by aspiring the whole sextet as one package toward itself if it is both tetravalent and electron-deficient, e.g. trifluoromethyl or trimethylammonio. Alternatively, the  $\pi$ -cloud will essentially remain stationary, as in chlorobenzene, or even be pushed away from lone-pair carrying substituents (with progressively increasing strength from fluorine to alkoxy to dialkylamino). In this way,  $\pi$ -electron density may accumulate at *meta* and *para* positions, where it counterbalances the already attenuated  $\sigma$ -polarization. In other words, the  $\pi$ -polarization may occur in either direction and does not necessarily fade away with distance (Figure 2).

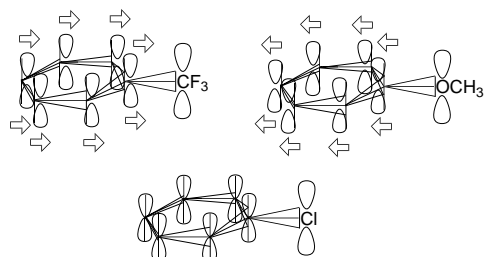


Figure 2. Possible directions of  $\pi$ -polarization according to the nature of the substituents.

Given this set of three model cases, where must we place the trifluoromethoxy group? Although smaller in magnitude, its  $\sigma$ -inductive effect is similar to the one caused by a fluorine or trifluoromethyl substituent. On the other hand, its  $\pi$ -donating capacity is dwarfed by that of the methoxy group, and seems to be even inferior to that of a fluorine atom. The blend of these two components confer its electronic individuality to the trifluoromethoxy group. While acidifying *ortho*-positions only moderately, its anion-stabilizing effect is retained at *meta*- and *para*-positions to a quite remarkable extent (Figure 3).

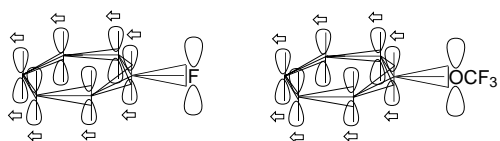


Figure 3. Direction of  $\pi$ -polarization for fluorobenzene and (trifluoromethoxy)benzene.

$\pi$ -Polarization (or  $\pi$ -cloud deformation) has previously been put forward to explain a variety of otherwise unintelligible phenomena.<sup>[22–27]</sup> Evidently, it has nothing in common with any “mesomeric” or “resonance” effect. Moreover, the reader will not have failed to notice the incompatibility of substituent effects as transpiring from the present work with Hammett or Taft type parameters.<sup>[28]</sup>

## Experimental Section

For working routine and abbreviations, see related publications from this laboratory.<sup>[30–32]</sup>  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded of samples dissolved in deuteriochloroform at 400 and 101 MHz, respectively, unless stated otherwise.

**Starting materials:** 4-(Trifluoromethoxy)anisole, fluorobenzene, and 2,2-difluoro-1,3-benzodioxole are commercially available. 1-(Trifluoromethoxy)naphthalene was prepared as previously described.<sup>[2]</sup>

**2-(Trifluoromethoxy)anisole:** Potassium carbonate (14 g, 0.10 mol) and methyl iodide (14 g, 6.2 mL, 0.10 mol) were added to a solution of 2-(trifluoromethoxy)phenol (18 g, 0.10 mol) in *N,N*-dimethylformamide (75 mL). The mixture was heated to 75 °C for 45 min before being distilled to give a colorless liquid. Yield: 17.4 g (91%); b.p. 69–70 °C/10 mmHg,  $n_D^{20} = 1.4364$ ;  $^1\text{H}$  NMR:  $\delta = 7.2$  (m, 2H), 6.99 (d,  $J = 8.1$  Hz, 1H), 6.80 (td,  $J = 7.9, 1.3$  Hz, 1H), 3.79 (s, 3H); elemental analysis calcd for  $\text{C}_8\text{H}_7\text{F}_3\text{O}_2$  (192.10): C 50.02, H 3.67; found C 49.91, H 3.94.

**3-(Trifluoromethoxy)anisole:** Prepared analogously from 3-(trifluoromethoxy)phenol (18 g, 0.10 mol), a colorless liquid was obtained upon distillation. Yield: 18.0 g (94%); b.p. 72–73 °C/10 mmHg,  $n_D^{20} = 1.4329$ ;  $^1\text{H}$  NMR:  $\delta = 7.28$  (t,  $J = 8.3$  Hz, 1H), 6.8 (m, 2H), 6.74 (s, 1H), 3.81 (s, 3H); elemental analysis calcd for  $\text{C}_8\text{H}_7\text{F}_3\text{O}_2$  (192.10): C 50.02, H 3.67; found C 50.21, H 3.60.

**Trapping products (Carboxylic Acids):** 2-Methoxybenzoic acid and 2-fluorobenzoic acid are commercially available. 2,2-Difluoro-1,3-benzodioxole-4-carboxylic acid<sup>[1]</sup> and 2-(trifluoromethoxy)benzoic acid<sup>[1]</sup> were prepared according to published procedures.

**1-Methoxy-2-naphthoic acid (1):** At –75 °C, potassium *tert*-butoxide (2.8 g, 25 mmol) was added to a solution of 1-methoxynaphthalene (3.9 g, 25 mmol) and *n*-butyllithium (25 mmol) in cyclohexane (16 mL) and tetrahydrofuran (50 mL). The mixture was stirred until homogeneous. After 2 h at –75 °C, it was poured onto an excess of freshly crushed dry ice. When the temperature of the mixture had risen to 25 °C, a 1.0 M aqueous solution (50 mL) of sodium hydroxide was added. The organic layer was decanted, and the aqueous phase was washed with diethyl ether (15 mL) before being acidified to pH 1 and extracted with diethyl ether (3  $\times$  30 mL). Evaporation of the solvent and crystallization of the residue from hexanes gave colorless needles. Yield: 4.1 g (81%); m.p. 126–127 °C (lit: 126–127 °C<sup>[33]</sup>);  $^1\text{H}$  NMR:  $\delta = 8.18$  (d,  $J = 8.3$  Hz, 1H), 8.10 (d,  $J = 8.5$  Hz, 1H), 7.92 (d,  $J = 8.2$  Hz, 1H), 7.74 (d,  $J = 8.5$  Hz, 1H), 7.6 (m, 2H), 4.17 (s, 3H).

**1-(Trifluoromethoxy)-2-naphthoic acid (2):** A solution of 1-(trifluoromethoxy)naphthalene (5.3 g, 25 mmol), *sec*-butyllithium (25 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA; 3.7 mL, 2.9 g, 25 mmol) in cyclohexane (15 mL) and tetrahydrofuran (50 mL) was kept for 2 h at –75 °C. Carboxylation, extraction (see above), and crystallization from ethyl acetate (12 mL) gave colorless cubes. Yield: 5.1 g (80%); m.p. 160–161 °C;  $^1\text{H}$  NMR:  $\delta = 8.3$  (m, 1H), 8.04 (d,  $J = 8.6$  Hz, 1H), 7.91 (d,  $J = 8.6$  Hz, 1H), 7.9 (m, 1H), 7.7 (m, 2H); elemental analysis calcd for  $\text{C}_{12}\text{H}_7\text{F}_3\text{O}_3$  (256.18): C 56.26, H 2.75; found C 56.27, H 2.99.

**1,3-Benzodioxole-4-carboxylic acid (4):** A solution containing 1,3-benzodioxole (3.9 g, 25 mmol) and *sec*-butyllithium (25 mmol) in pentanes (17 mL) and tetrahydrofuran (50 mL) was kept for 2 h at –100 °C before being poured onto an excess of freshly crushed dry ice. The organic materials were extracted and neutralized as described above for acid **1**. Crystallization from hexanes afforded 0.33 g (12%) of catechol **3** (1,2-dihydroxybenzene). After evaporation of the mother liquor and crystallization of the residue from a 1:10 (v/v) mixture of ethyl acetate and hexanes, the pure acid **2** was collected as colorless prisms. Yield: 3.2 g

(63 %); m.p. 230–231 °C (lit: 230–233 °C<sup>[34]</sup>); <sup>1</sup>H NMR:  $\delta$  = 7.46 (dd,  $J$  = 8.2, 1.1 Hz, 1H), 7.01 (dd,  $J$  = 7.9, 1.2 Hz, 1H), 6.89 (t,  $J$  = 7.9 Hz, 1H), 6.13 (s, 2H).

**3-Methoxy-2-(trifluoromethoxy)benzoic acid (5):** 2-(Trifluoromethoxy)-anisole (4.8 g, 25 mmol), *sec*-butyllithium (25 mmol) and *N,N,N',N',N''*-pentamethylethylenetriamine (4.3 g, 5.0 mL, 25 mmol) in hexanes (16 mL) and tetrahydrofuran (50 mL) were stored for 2 h at –75 °C. The mixture obtained after carboxylation was worked up as described above to afford a 1:10 mixture of 2-methoxy-3-(trifluoromethoxy)benzoic acid (6) and 3-methoxy-2-(trifluoromethoxy)benzoic acid (5); crude yield: 4.7 g (79 %). Isomer 5 crystallized from hexanes as colorless prisms. Yield: 4.0 g (68 %); m.p. 127–128 °C; <sup>1</sup>H NMR:  $\delta$  = 7.58 (d,  $J$  = 8.1 Hz, 1H), 7.38 (t,  $J$  = 8.0 Hz, 1H), 7.23 (d,  $J$  = 8.0 Hz, 1H), 3.93 (s, 3H); elemental analysis calcd for C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>O<sub>4</sub> (236.15): C 45.78, H 2.98; found C 45.66, H 3.02.

When the same reaction was performed by employing simply *sec*-butyllithium as metalating agent, a 1:1 mixture of acids 5 and 6 was obtained; crude yield: 4.6 g (78 %).

**2-Methoxy-3-(trifluoromethoxy)benzoic acid (6):** 2-(Trifluoromethoxy)-anisole (4.8 g, 25 mmol) in tetrahydrofuran (50 mL) was treated with *tert*-butyllithium (25 mmol) in pentane (17 mL) for 2 h at –75 °C. Upon carboxylation, extraction, and neutralization, a 4:1 mixture of 2-methoxy-3-(trifluoromethoxy)benzoic acid (6) and 3-methoxy-2-(trifluoromethoxy)benzoic acid (5) was obtained; crude yield: 4.8 g (81 %). The pure isomer 6 was obtained by crystallization from hexanes as colorless prisms. Yield: 2.9 g (49 %); m.p. 79–80 °C; <sup>1</sup>H NMR:  $\delta$  = 8.10 (dd,  $J$  = 7.9, 1.2 Hz, 1H), 7.55 (d,  $J$  = 8.1 Hz, 1H), 7.31 (t,  $J$  = 7.9 Hz, 1H), 4.12 (s, 3H); elemental analysis calcd for C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>O<sub>4</sub> (236.15): C 45.78, H 2.98; found C 45.66, H 3.02.

**2-Methoxy-6-(trifluoromethoxy)benzoic acid (7):** In an analogous reaction, 3-(trifluoromethoxy)anisole (4.8 g, 25 mmol) was treated with *sec*-butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (50 mL) for 2 h at –100 °C. Carboxylation gave the pure acid 7 as colorless prisms. Yield: 5.4 g (91 %); m.p. 92–93 °C (from hexanes); <sup>1</sup>H NMR:  $\delta$  = 7.43 (t,  $J$  = 8.5 Hz, 1H), 6.96 (d,  $J$  = 8.4 Hz, 1H), 6.91 (d,  $J$  = 8.5 Hz, 1H), 3.92 (s, 3H); elemental analysis calcd for C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>O<sub>4</sub> (236.15): C 45.78, H 2.98; found C 45.77, H 2.65.

**5-Methoxy-2-(trifluoromethoxy)benzoic acid (8):** Carboxylation of a reaction mixture containing 4-(trifluoromethoxy)anisole (4.8 g, 25 mmol), *sec*-butyllithium (25 mmol) and *N,N,N',N',N''*-pentamethylethylenetriamine (4.3 g, 5.0 mL, 25 mmol) in hexanes (15 mL) and tetrahydrofuran (50 mL), which was kept for 2 h at –75 °C, afforded a 1:1 mixture of 5-methoxy-2-(trifluoromethoxy)benzoic acid (8) and 2-methoxy-5-(trifluoromethoxy)benzoic acid (9); yield: 4.6 g (78 %). Isomer 9 (see below) was removed by fractional crystallization from hexanes. After the evaporation of the mother liquor, the residue was repetitively crystallized

from methanol at –75 °C to give a small amount of the pure acid 8 as colorless prisms. Yield: 0.5 g (8 %); m.p. 49–52 °C; <sup>1</sup>H NMR:  $\delta$  = 7.53 (d,  $J$  = 0.9 Hz, 1H), 7.26 (d,  $J$  = 8.0 Hz, 1H), 7.09 (dd,  $J$  = 7.9, 1.0 Hz, 1H), 3.85 (s, 3H); elemental analysis calcd for C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>O<sub>4</sub> (236.15): C 45.78, H 2.98; found C 45.78, H 3.08.

**2-Methoxy-5-(trifluoromethoxy)benzoic acid (9):** This product was analogously made from 4-(trifluoromethoxy)anisole (4.8 g, 25 mmol) by its consecutive reaction with *tert*-butyllithium (25 mmol) in pentanes (17 mL) and tetrahydrofuran (50 mL) kept for 2 h at –75 °C and poured onto dry ice. It was isolated as described above to give colorless prisms. Yield: 5.2 g (88 %); m.p. 63–65 °C (from hexanes); <sup>1</sup>H NMR:  $\delta$  = 8.02 (d,  $J$  = 2.8 Hz, 1H), 7.45 (dd,  $J$  = 8.9, 2.9 Hz, 1H), 7.10 (d,  $J$  = 9.0 Hz, 1H), 4.08 (s, 3H); elemental analysis calcd for C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>O<sub>4</sub> (236.15): C 45.78, H 2.98; found C 45.70, H 3.07.

When the same reaction was performed by employing simply *sec*-butyllithium as metalating agent, a 1:9 mixture of acids 8 and 9 was obtained; crude yield: 5.1 g (86 %).

**Competition kinetics:** The competition experiments were performed and evaluated as recently described.<sup>[8]</sup> The rate ratios  $k_A/k_B$  were calculated by inserting the amounts of the two competing substrates A and B before and after their reaction with *sec*-butyllithium in the standard formula  $k_A/k_B = \ln([A]_0/[A]_t)/\ln([B]_0/[B]_t)$ .<sup>[9–10]</sup> The initial amounts  $[A]_0$  and  $[B]_0$  were found by weighing in. The amounts of unconsumed substrates  $[A]_t$  and  $[B]_t$  were directly determined by gas chromatography after the reaction by using an internal standard for calibration. As a control, they were also indirectly determined, again quantified by gas chromatography, by subtraction of all identified products; in particular, the methyl esters obtained after quenching the reaction with dry ice, subsequent neutralization and exhaustive treatment with diazomethane; in addition some catechol was formed whenever 1,3-benzodioxole was employed as a substrate. The details are numerically listed (Table 4), and the reactivity differences illustrated in scalar form (Figure 1).

**Error estimation:** We assume the relative rates  $k_A/k_B$  to be afflicted with an average error of less than 10% (presumably around 5%) as long as the ratios do not exceed 10. This estimate is based on numerous repetitive experiments carried out to check the reproducibility of the results obtained. In addition, the competition reactions also included, where possible, overlapping reactivity comparisons (see Figure 1).

**General competition protocol:** Pairs of substrates A and B (approximately 2.5 mmol each) and of the “internal standard” undecane (1.0 mmol), were dissolved in tetrahydrofuran (10 mL). A few drops of this mixture were kept aside for later gas chromatographic analysis before the rest was transferred into a 0.25 L Schlenk vessel and cooled to –75 °C (or –100 °C, where specified). A commercial solution of *sec*-butyllithium (2.5 mmol) in hexanes (1.6 mL) was added. After 45 min at –75 °C (or –100 °C), the

Table 4. Relative reaction rates  $k_A/k_B$  (without statistic correction) calculated with the amounts of two competing substrates A and B before ( $[A]_0$  and  $[B]_0$ ) and after ( $[A]_t$  and  $[B]_t$ ) their simultaneous reaction with *sec*-butyllithium in tetrahydrofuran at –75 °C.

Substrate A	Substrate B	$[A]_0$	$[B]_0$	$[A]_t^d$	$[A]_t^i$ [a]	$[B]_t^d$	$[B]_t^i$ [a]	$k_A/k_B$
F <sub>2</sub> BDX [b]	<i>m</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	2.50	2.48	1.10	(1.17)	1.88	(1.94)	3.0 <sup>[d]</sup>
<i>m</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	<i>p</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	2.30	2.36	0.71	(0.75)	1.89	(1.93)	5.3 <sup>[d]</sup>
<i>p</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	FC <sub>6</sub> H <sub>5</sub>	2.48	2.54	0.80	(0.82)	2.25	(2.32)	9.3
<i>p</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	F <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	2.51	2.56	0.39	(0.42)	2.34	(2.35)	20.7
FC <sub>6</sub> H <sub>5</sub>	F <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	2.49	2.57	1.42	(1.45)	2.00	(2.00)	2.2
F <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	1-F <sub>3</sub> COC <sub>10</sub> H <sub>7</sub> <sup>[c]</sup>	2.48	2.53	1.48	(1.50)	1.99	(2.02)	2.2
F <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	<i>o</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	2.47	2.45	0.99	(1.02)	2.06	(2.05)	5.2
F <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	H <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	2.48	2.60	1.17	(1.24)	2.42	(2.45)	10.5
1-F <sub>3</sub> COC <sub>10</sub> H <sub>7</sub> <sup>[c]</sup>	BDX <sup>[e]</sup>	2.52	2.72	1.79	(1.84)	2.01	(2.08)	1.1 <sup>[d]</sup>
1-F <sub>3</sub> COC <sub>10</sub> H <sub>7</sub> <sup>[c]</sup>	<i>o</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	2.51	2.57	1.83	(1.85)	2.22	(2.26)	2.2
BDX <sup>[e]</sup>	<i>o</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	2.60	2.48	1.85	(1.92)	2.11	(2.12)	2.1 <sup>[d]</sup>
BDX <sup>[e]</sup>	H <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	2.48	2.50	1.12	(1.19)	2.26	(2.27)	7.9 <sup>[d]</sup>
<i>o</i> -F <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	H <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	2.44	2.54	0.99	(1.01)	1.93	(2.00)	3.3
H <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	1-H <sub>3</sub> COC <sub>10</sub> H <sub>7</sub> <sup>[f]</sup>	2.58	2.52	1.25	(1.33)	2.06	(2.15)	3.6

[a]  $[A]_t^i$  and  $[B]_t^i$  stand for the amount of substrates A and B present after the reaction as directly determined by gas chromatography whereas  $[A]_t^d$  and  $[B]_t^d$  are indirectly determined by subtracting from the initial amounts  $[A]_0$  and  $[B]_0$  the amount of the products (the methyl esters obtained after carboxylation, neutralization, and treatment with diazomethane; in addition catechol when 1,3-benzodioxole served as a substrate) obtained after the reaction and quantified again by gas chromatography. [b] F<sub>2</sub>-BDX = 2,2-difluoro-1,3-benzodioxole. [c] 1-F<sub>3</sub>COC<sub>10</sub>H<sub>7</sub> = 1-(trifluoromethoxy)naphthalene. [d] At –100 °C rather than at –75 °C. [e] BDX = 1,3-benzodioxole. [f] 1-H<sub>3</sub>COC<sub>10</sub>H<sub>7</sub> = 1-methoxynaphthalene.

reaction mixture was poured onto an excess of freshly crushed dry ice. Once all the carbon dioxide had evaporated, a known amount of a second "internal standard" (benzoic acid) was added. The organic layer was extracted with an aqueous solution of sodium hydroxide (1.0 M, 3 × 10 mL), and washed with brine (2 × 10 mL), before being examined by gas chromatography. The peak areas of substrates A and B relative to those of the neutral standard, before and after treatment with *sec*-butyllithium, were listed and were used to calculate the rate ratios ( $k_A/k_B$ ). The combined aqueous layers were acidified (to ~pH 1) and extracted with diethyl ether (3 × 25 mL). The organic phase was treated with ethereal diazomethane until the yellow color persisted. The concentrations of the A<sub>H</sub>- and B<sub>H</sub>-derived esters (A<sub>E</sub> and B<sub>E</sub>) were determined by gas chromatographic comparison of their peak areas with that of the methyl ester of the alkali-soluble "internal standard"; unequal detector sensitivities for the various esters were corrected by calibration factors. In each case it was ascertain that the consumption of substrates A and B was counterbalanced by the formation of esters A<sub>E</sub> and B<sub>E</sub> in corresponding quantities.

**Conditions of gas chromatographic analysis:** As a rule, two columns of different polarity were used to probe the concentrations of substrates and products. Different conditions had to be employed for the substrates [30 m, DB-wax, 30 °C (5 min) → 100 °C (10 min), heating rate 25 °C min<sup>-1</sup>; 30 m, DB-23, 30 °C (5 min) → 100 °C (10 min), heating rate 25 °C min<sup>-1</sup>] and the methyl esters products (30 m, DB-wax, 150 °C; 30 m, DB-23, 150 °C).

### Acknowledgement

This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grants 2-293-74, 2-467-75 and 20-49/307-96).

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Received: July 25, 2001 [F 3443]