DOI: 10.1002/ejoc.200600350

Proton Mobility in 2-Substituted 1,3-Dichlorobenzenes: "*ortho*" or "*meta*" Metalation?

Manfred Schlosser,*[a,b] Christophe Heiss,[a] Elena Marzi,[a] and Rosario Scopelliti[a]

Keywords: Buttressing effects / Kinetic CH acidities / Metalation / Regioselectivity / Steric repulsion

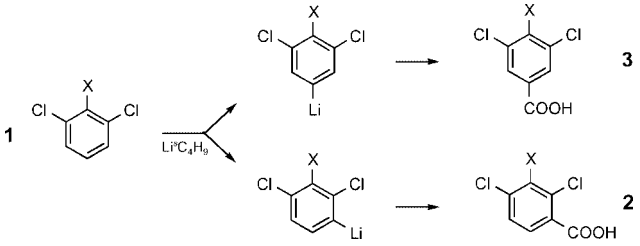
Nine 1,3-dichlorobenzene congeners were selected as model compounds to assess the relative rates of proton abstraction from 4- and 5-positions ("*ortho*" vs. "*meta*" metalation). Using lithium 2,2,6,6-tetramethylpiperidide as the basic reagent, the chlorine-adjacent 4-position underwent metalation exclusively. In contrast, attack at the chlorine-remote 5-position became significant even in the case of moderately sized 2-substituents (such as dimethylamino or ethyl) when *sec*-butyllithium was employed. The "*ortho*/*para*" (4-/5-) ratios ranged from 80:20 to 65:35. The more pronounced "*meta*-orienting" effect of silicon as opposed to carbon substituents can be attributed to dissimilarities in the π polarization of the aromatic ring.

Introduction

(2,6-Dichlorophenyl)trialkylsilanes and (2,6-dibromophenyl)trialkylsilanes have been found to undergo mainly or exclusively proton abstraction from the halogen-remote 4-position rather than from the halogen-adjacent 3-position.[1,2] We have attempted to rationalize this preference of "*meta* metalation" over "*ortho* metalation" on the basis of repulsive interactions between bonding and nonbonding electrons of the halogen atoms and the delocalized electrons mediating the proton transfer from the aromatic carbon atom to the base.[3] However, so far the question has not yet been addressed whether this "buttressing phenomenon"[1,2] imperatively requires the presence of a trialkylsilyl group at the site flanked by the two halogen atoms or if the latter could be replaced by any other, more or less space-filling non-hydrogen substituent.

Results

To examine this issue we have selected nine new model compounds **1** harboring small and middle-sized groups at the 2-position. These substrates were treated with *sec*-butyllithium in tetrahydrofuran at –75 °C before the intermediates were quenched with dry ice. The product composition was probed by NMR spectroscopy and, after conversion of the free carboxylic acids obtained into the more volatile methyl esters, by gas chromatography. The structures of the regioisomers **2** and **3** (Scheme 1) were assigned on the basis of their spectral characteristics and, whenever possible, by retention-time comparison with separately prepared, authentic samples.



Scheme 1. Metalation and subsequent carboxylation of 2-X-substituted 1,3-dichlorobenzenes (**1**) with *sec*-butyllithium giving rise to mixtures of 2,4-dichloro-3-X-benzoic acids (**2**) and 3,5-dichloro-4-X-benzoic acids (**3**).

As the data compilation shows (Table 1), in all cases, except one, "*meta* metalation" derived isomers **3** were formed along with the "*ortho* metalation" derived isomers **2**, the main component. Only 1,3-dichloro-2-fluorobenzene (**1a**) gave virtually no detectable amount of 3,5-dichloro-4-fluorobenzoic acid (**3a**). The small and electronegative substituents chloro (**b**), methoxy (**c**) and (lithiated) *tert*-butoxycarboxamido (**f**) produced large "*ortho*/*meta*" (**2**/**3**) ratios of ≥ 95:5 and the triethylsilyloxy entity (**d**) still of ≥ 90:10. The more bulky dimethylamino and the carbon-attached methyl, ethyl and trifluoromethyl groups directed the attack of the metalating reagent to the chlorine-adjacent and chlorine-remote positions in ratios ranging from 80:20 to 75:25 (Table 1).

[a] Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale, BCh,
1015 Lausanne, Switzerland
Fax: +41-21-6939365
E-mail: manfred.schlosser@epfl.ch
[b] Université de Lausanne,
1015 Lausanne, Switzerland

Table 1. Consecutive metalation[a] and carboxylation of 2-X-substituted 1,3-dichlorobenzenes (**1**), including (2,6-dichlorophenyl)triethylsilane (**1j**) for comparison: combined yields and "*ortho*/*meta*-metalation" ratios of acids **2** and **3**.

Compound label	2-Substituent X	Yield (%)[b]	*ortho*/*meta* ratio (acids **2**/**3**)
a	F	18[c]	100:0
b	Cl	14[d]	96:4
c	OCH_3	85	97:3
d	$OSi(C_2H_5)_3$	70	91:9
e	$N(CH_3)_2$	62	75:25
f	$NLiCOOC(CH_3)_3$	56	95:5[e]
g	CH_3	18[f]	80:20
h	C_2H_5	77	75:25
i	CF_3	25[g]	75:25
j	$Si(C_2H_5)_3$[2]	85[h]	26:74

[a] Using *sec*-butyllithium in tetrahydrofuran at –75 °C as the metalating reagent. [b] Combined yields of acids **2** and **3**. [c] Along with 71% of 3-chloro-2-fluorobenzoic acid. [d] Along with 5.7% of 2,3-dichlorobenzoic acid and 67% of 2,6-dichlorobenzoic acid. [e] Acids **2f** and **3f**: X = $NHCOOC(CH_3)_3$ rather than $NLiCOOC(CH_3)_3$. [f] Along with 71% of (2,6-dichlorophenyl)acetic acid. [g] Along with 36% of 3-chloro-2-(trifluoromethyl)benzoic acid. [h] Along with 6.4% of 3-chloro-2-(trimethylsilyl)benzoic acid.

With 1,3-dichloro-2-fluorobenzene (**1a**), 1,2,3-trichlorobenzene (**1b**) and 2,6-dichloro-4-(trifluoromethyl)benzene (**1i**) as the substrates, the predominant reaction mode was permutational chlorine/lithium interconversion rather than *ortho*- or *meta*-metalation. No such side reaction was encountered when lithium 2,2,6,6-tetramethylpiperidide (LITMP) served as the base, lithium amides being generally unable to promote halogen/metal permutations.[4] Moreover, exclusively *ortho*-deprotonation occurred (at the 4-position) and never *meta*-deprotonation (at the 5-position) when LITMP was employed. Being a less powerful reagent than *sec*-butyllithium, it apparently has no other choice than to produce just the most stable (i.e., least basic) organolithium intermediate.[5] On the other hand, LITMP attacked 2,6-dichlorotoluene unselectively at both the benzylic methyl group and at the aromatic ring in a proportion of 75:25. Again, unlike *sec*-butyllithium and other alkyllithium compounds, it generated only *ortho*-lithiated and not a trace of *meta*-lithiated species.

Discussion

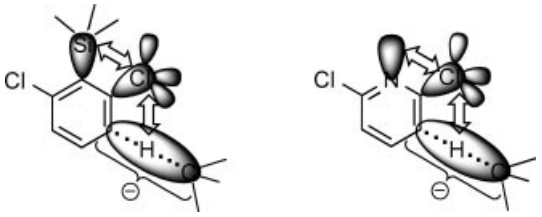
Buttressing effects compromising the *ortho*-metalation of (2,6-dibromophenyl)trialkylsilanes,[1,2] (2,6-dichlorophenyl)-trialkylsilanes[1,2] and even (2,6-difluorophenyl)trialkylsilanes[6] have been discovered a short while ago. So far, this mysterious phenomenon seemed to be restricted to substrates carrying very bulky substituents, in particular trialkylsilyl groups, as emitters and neighboring halogen atoms or trifluoromethyl groups as transmitters of steric pressure.[7,8] It is surprising if not alarming to recognize now that clean *ortho*-metalatation is also menaced with substrates as simple as 1,3-dichloro-2-ethylbenzene or 2,6-dichloro-*N*,*N*-dimethylaniline if *sec*-butyllithium or other alkyllithium compounds serve as the reagent. Obviously, buttressing effects retarding *ortho*-metalation are more common than thought before. Future synthetic work relying on neighboring group-assisted metalations will have to account for them as a possible complication.

Of course there are still differences in the numbers that need to be explained. The highest *meta*/*ortho* ratio found in the present study (Table 1) approximates 1:3 whereas in the silane series it ranges from 3:1 to >50:1, depending on the metalation conditions. There is one immediately intelligible reason why trialkylsilyl should be more potent than ethyl and presumably also isopropyl or *tert*-butyl in impeding the deprotonation of the vacant position adjacent to a chlorine atom. Behaving as σ-inductive electron donors, alkyl groups tend to push away the aromatic sextet and, by accumulating electron density at positions across the ring, deactivate the latter toward base attack. Metalation of *tert*-butylbenzene at *meta* and *para* positions is significantly disfavored relative to benzene, the reference compound. The partial rate factors k_m^f and k_p^f amount to 0.30 and 0.45, respectively, in tetrahydrofuran.[9,10] The metalation of (triisopropyl)-phenylsilane is equally retarded at the *meta* position (k_m^f = 0.35) but accelerated, if only slightly (k_p^f = 1.05), at the *para* position.[9] This divergence is caused by the different polarization of the aromatic π sextet imposed by silyl substituents. Although still acting as weak σ donors,[11] they are potent π-electron attractors.[12,13] Pulling excess charge in their vicinity, they deplete the remote *para* position of electron density. Consequently, a (2,6-dichlorophenyl)trialkylsilane should undergo metalation at its 4-position (*para* with respect to Si, *meta* with respect to Cl) approximately ten times faster than 1,3-dichloro-2-ethylbenzene or, by extension, 2-*tert*-butyl-1,3-dichlorobenzene do at the 5-position (*para* with respect to the alkyl group, *meta* with respect to Cl).

There may be a second factor privileging *meta*- rather than *ortho*-deprotonation of (2,6-dichlorophenyl)trialkylsilanes. The buttressing transmission capacity increases with the size of the halogen (F < Cl < Br < I).[7] Presumably also the size of the emitter plays a crucial role. The repulsive force should increase with the stretching of the path along which two neighboring groups enter into collision. In other words, the longer the bonds, the stronger the substituents are tied up in their respective positions. Bond length correlates inversely with bond strength and electron density. A C–Si orbital being bigger and more diffuse than a C–C orbital, electrons residing in the former may more potently interact with the neighboring carbon–halogen bonds and the halogen lone pairs and, as a corollary, shield the adjacent positions more effectively.

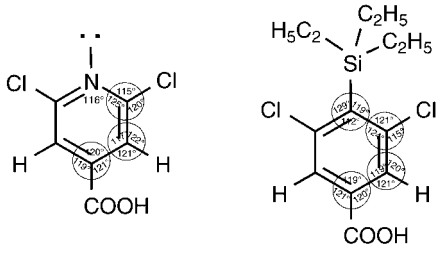
To correlate the magnitude of repulsion between the strain transmitting substituent (e. g., chlorine) and the strain emitting substituent (e.g., trialkylsilyl) on one hand and the strain transmitting substituent and the proton-delivering array on the other hand with the diffusiveness of the orbitals involved, is at present hardly more than a tentative idea. However, this working hypothesis also throws a new light on the peculiar regioselectivity of the 2,6-dichlo-

ropyridine metalation. Butyllithium abstracts protons concomitantly from the 3- ("*ortho*") and 4- ("*meta*") positions in a ratio of 1:4.[14,15] The preference for the 4-position can only partially be imputed to the intrinsic site acidities which increase in pyridine with increasing distance from the hetero center (2- < 3- < 4-).[16–19] Besides this, the diffuse lone pair at the nitrogen atom appears to exert a strong buttressing effect and thus discriminates against base attack on the 3-position (Scheme 2).



Scheme 2. Repulsion between the diffuse C–Si bond or the diffuse pyridine lone pair and the C–Cl bond and its relay transmission to the proton-transfer array.

A fact of fundamental importance should be emphasized once more. Buttressing effects on proton mobility are kinetic in nature.[3] They manifest themselves at the level of transition states rather than of ground states. In line with this, lithium diisopropylamide converts 2,6-dichloropyridine to a 9:1 mixture of 3- and 4-lithiated intermediates.[14] This means, the thermodynamically more stable species predominates clearly under acid–base equilibrating conditions. Moreover, the crystalline 2,6-dichloropyridine-4-carboxylic acid exhibits perfectly normal bond angles which prove to be even less distorted than those of 3,5-dichloro-4-(triethylsilyl)benzoic acid[3] (Scheme 3).



Scheme 3. Crystallographic structures of solid derivatives of 2,6-dichloropyridine and (2,6-dichlorophenyl)triethylsilane (all bond angles being rounded and, at C-2 and C-3, symmetry-averaged).

Experimental Section

Generalities: For working routine and abbreviations, see related publications from this laboratory.[20–22] Unless specified otherwise, the ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, of samples dissolved in deuteriochloroform.

Crystallography: 2,6-Dichloropyridine-4-carboxylic acid was prepared by butyllithium-promoted metalation followed by carboxylation, neutralization and crystallization of 2,6-dichloropyridine.[15] X-ray diffraction data were collected using the Mo-K_α (0.71073 Å) radiation and a low temperature device [T = 140(2) K] with a four-circle Kappa goniometer, equipped with an Oxford Diffraction KM4 Sapphire CCD. Data reductions were performed with the CrysAlis RED 1.7.0 software (Oxford Diffraction, Abingdon, UK, 2003). Semi-empirical absorption correction has been applied to the data sets. The structure was refined using the full-matrix least-squares on F^2 with all non-hydrogen atoms anisotropically defined. The hydrogen atoms were obtained from the electron-density map and then refined as isotropic. Structure solution, structure refinement and geometrical calculations were carried out with the SHELXTL software (University of Göttingen, 1997; Bruker AXS, Madison, 1997). CCDC 601781 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1. Starting Materials: The commercially available substrates **1a**, **1b**, **1c** and **1d** were purchased from the respective suppliers (Aldrich, Buchs; Apollo Scientific, Stockport; Fluka, Buchs). The others were prepared as described below or following literature procedures a specified.

(2,6-Dichlorophenoxy)triethylsilane (1d): 2,6-Dichlorophenol (12 g, 50 mmol), (chloro)triethylsilane (13 mL, 11 g, 75 mmol) and triethylamine (10.5 mL, 7.6 g, 75 mmol) in tetrahydrofuran (0.15 L) were heated for 12 h at 50 °C. Upon direct distillation a colorless oil was collected; b.p. 48–50 °C/0.6 Torr; n_D^{20} = 1.5421; d_4^{20} = 1.389; yield 18.5 g (89%). ^{1}H NMR: δ = 7.24 (d, J = 8.0 Hz, 2 H), 6.82 (t, J = 7.7 Hz, 1 H), 1.0 (m, 9 H), 0.8 (m, 6 H) ppm. ^{13}C NMR: δ = 149.0, 128.4 (2 C), 126.9 (2 C), 121.9, 6.6 (3 C), 5.6 (3 C) ppm.

(2,6-Dichlorophenyl)ethane (1h): 1,3-Dichlorobenzene (11 mL, 15 g, 0.10 mol) was added to a solution of *sec*-butyllithium (0.10 mol) in cyclohexanes (80 mL) and tetrahydrofuran (0.12 L) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the reaction mixture was treated with a precooled solution of diethyl sulfate (16 mL, 19 g, 0.12 mol) in tetrahydrofuran. Direct distillation afforded a colorless oil; b.p. 55–57 °C/1 Torr (ref.[23] b.p. = 207.5 °C/760 Torr). n_D^{20} = 1.5435 (ref.[23] n_D^{20} = 1.5438); d_4^{20} = 1.241; yield 16 g (90%).

1,3-Dichloro-2-(trifluoromethyl)benzene (1i): Potassium fluoride (6.4 g, 0.11 mol) and cuprous iodide (21 g, 0.11 mol) were mixed and flame-heated under gentle shaking at reduced pressure (1 Torr) until a yellow-greenish color appeared. Anhydrous *N*-methylpyrrolidone (0.10 L), 2,6-dichloroiodobenzene (see the following paragraph; 28 g, 0.10 mol) and trimethyl(trifluoromethyl)silane (15 mL, 14 g, 0.10 mol) were added consecutively. The brown solution thus obtained was heated at 50 °C for 6 h before the solution was poured into 6.4 M aqueous ammonia (0.20 L). The product was extracted with diethyl ether (3 × 0.10 L) and the combined organic layers were washed with 6.4 M aqueous ammonia (3 × 50 mL) and brine (0.10 L), dried and the solvents evaporated. Upon distillation, a colorless liquid was obtained; b.p. 62–63 °C/9 Torr; n_D^{20} = 1.4921; d_4^{20} = 0.805; (ref.[24]: no physical constants or analysis reported); yield 14.9 g (69%). ^{1}H NMR: δ = 7.43 (d, J = 8.1 Hz, 2 H), 7.35 (t, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 134.5 (s), 132.3 (s, 2 C) ppm; 130.7 (s, 2 C), 126.1 (q, J = 30 Hz), 122.7 (q, J = 276 Hz) ppm. ^{19}F NMR: δ = –56.2 ppm. MS (C.I.): m/z (%) = 216 (59) [M$^+$ + 1], 215 (14) [M$^+$], 214 (100). $C_7H_3Cl_2F_3$ (215.00): calcd. C 42.79, H 1.80; found C 42.73, H 1.74.

1,3-Dichloro-2-iodobenzene: At –75 °C, 1,3-dichlorobenzene (12 mL, 15 g, 0.10 mol) was added to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.14 L) and hexanes (70 mL). After 2 h at this temperature, the reaction mixture was treated with a solution of iodine (25 g, 0.10 mol) in tetrahydrofuran (0.10 L) before being poured into a saturated solution of sodium thiosulfate (0.10 L) and extracted with diethyl ether (3 × 0.10 L). After evaporation of the volatiles, the residue was crystallized from methanol; colorless needles; m.p. 68–69 °C (ref.[25] m.p. 67.2–67.6 °C); yield

26.7 g (98%). ^{1}H NMR: δ = 7.32 (d, J = 8.0 Hz, 2 H), 7.20 (t, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 140.6 (s, 2 C), 129.6 (s), 127.2 (s, 2 C), 103.7 (s) ppm. MS (C.I.): *m*/*z* (%) = 274 (60) [M^+ + 1], 273 (11) [M^+], 272 (100), 127 (13).

2. Separately Prepared Benzoic Acids for Comparison: 2,3-Dichlorobenzoic acid[26] (m.p. 165–166 °C) and 2,6-dichlorobenzoic acid[1] (m.p. 142–144 °C) were prepared in 88% and 95% yield, respectively, by the reaction of 1,2- and 1,3-dichlorobenzene with 1.6 M butyllithium in tetrahydrofuran for 2 h at –75 °C followed by carboxylation with dry ice and neutralization. 3,4,5-Trichlorobenzoic acid was made from 1,2,3-trichlorobenzene by a sequence of transformations featuring metalation, bromination, heavy-halogen migration and "chemical cleaning" processes as previously exemplified with 1,2,3-trifluorobenzene.[27,28]

Trimethyl(2,3,4-trichlorophenyl)silane: Diisopropylamine (28 mL, 20 g, 0.20 mol) and 1,2,3-trichlorobenzene (36 g, 0.20 mol) were added consecutively to a solution of butyllithium (0.20 mol) in hexanes (0.12 L) and tetrahydrofuran (0.30 L) cooled in a dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was treated with chloro(trimethyl)silane (26 mL, 22 g, 0.20 mol), acidified with 2.0 M hydrochloric acid (0.10 L) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried and concentrated. Distillation of the residue afforded a colorless oil; b.p. 80–82 °C/1 Torr; n_D^{20} = 1.4547; d_4^{20} = 1.112; yield 45.3 g (89%). ^{1}H NMR: δ = 7.34 (d, J = 8.0 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 0.34 (s, 9 H) ppm. $C_9H_{11}Cl_3Si$ (253.60): calcd. C 42.67, H 4.34; found C 42.68, H 4.20.

2,3,4-Trichloro-1,5-phenylenebis(trimethylsilane): Diisopropylamine (20 mL, 16 g, 0.15 mol) and trimethyl(2,3,4-trichlorophenyl)silane (38 g, 0.15 mol) were added consecutively to a solution of butyllithium (0.15 mol) in hexanes (90 mL) and tetrahydrofuran cooled in a dry ice/methanol bath. After 2 h at –75 °C, the mixture was treated with chloro(trimethyl)silane (20 mL, 16 g, 0.15 mol), washed with brine (0.10 L) and extracted with diethyl ether (3 × 50 mL). After evaporation of the volatiles, tiny colorless needles were collected; m.p. 71–73 °C (from acetone); yield 43.5 g (89%). ^{1}H NMR: δ = 7.40 (s, 1 H), 0.38 (s, 18 H) ppm. $C_{12}H_{19}Cl_3Si_2$ (325.64): calcd. C 44.25, H 5.81; found C 44.27, H 6.05.

1,5-Dibromo-2,3,4-trichlorobenzene: The bis(silane) (33 g, 0.10 mol) and bromine (42 mL, 0.13 kg, 0.80 mol) were heated in refluxing tetrachloromethane (30 mL) for 12 h. The mixture was washed with a saturated aqueous solution (0.10 L) of sodium sulfite before being evaporated. Crystallization from chloroform gave big colorless needles; m.p. 110–112 °C; yield 32.6 g (96%). ^{1}H NMR: δ = 7.88 (s) ppm. $C_6HBr_2Cl_3$ (339.24): calcd. C 21.24, H 0.30; found C 21.21, H 0.15.

1,2-Dibromo-3,4,5-trichlorobenzene: Diisopropylamine (5.0 g, 50 mmol) and 1,5-dibromo-2,3,4-trichlorobenzene (17 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (70 mL) cooled in a dry ice/methanol bath. After 2 h at –75 °C, the mixture was poured into 2.0 M hydrochloric acid (20 mL) and extracted with diethyl ether (3 × 50 mL). Upon evaporation of the combined organic layers a colorless solid was isolated. It was composed of the starting material 1,5-dibromo-2,3,4-trichlorobenzene and the isomeric 1,2-dibromo-3,4,5-trichlorobenzene in a 1:1 ratio as revealed by gas chromatographic analysis (2 m, 2% FFAP, 150 °C; 2 m, 2% OV-17, 180 °C); yield 15.0 g (89%).

5-Bromo-1,2,3-trichlorobenzene: Some part (6.5 g, 20 mmol) of the 1:1 mixture described in the preceding paragraph was dissolved in tetrahydrofuran (40 mL) and precooled before being added to butyllithium (20 mmol) in hexanes (11 mL) and diethyl ether (0.20 L) kept at –100 °C. After 15 min, the reaction mixture was neutralized with 2.0 M hydrochloric acid and extracted with diethyl ether (2 × 20 mL). The colorless solid obtained after evaporation of the volatiles was composed of 1-bromo-2,3,4-trichlorobenzene and 5-bromo-1,2,3-trichlorobenzene in a 1:1 ratio as evidenced by gas chromatography (2 m, 2% FFAP, 200 °C; 2 m, 2% OV-17, 200 °C); yield 4.9 g (94%). This isomeric mixture (3.9 g, 15 mmol) was dissolved in diethyl ether (15 mL) and, when precooled, rapidly added to a stoichiometrically insufficient amount of butyllithium (7.5 mmol) in hexanes (4.0 mL) and diethyl ether (75 mL) kept at –100 °C. After 15 min at this temperature, the reaction mixture was washed with dilute hydrochloric acid (25 mL) and brine (25 mL) and the solvents evaporated. Crystallization from hexanes afforded colorless needles; m.p. 56–58 °C (ref.[29] 56 °C); yield 4.9 g (49%). ^{1}H NMR: δ = 7.56 (s) ppm.

3,4,5-Trichlorobenzoic Acid (3b): 5-Bromo-1,2,3-trichlorobenzene (1.30 g, 5.0 mmol) was added to a solution of butyllithium (5.0 mmol) in hexanes (3.0 mL) and tetrahydrofuran (5.0 mL) kept in a dry ice/methanol bath. After 15 min at –75 °C, the mixture was poured on an excess of freshly crushed dry ice and, when at +25 °C, acidified with a 2.0 M ethereal solution (5.0 mL) of hydrogen chloride. The solvents were stripped off and the residue extracted with boiling pentanes (3 × 10 mL). Upon concentration and cooling, colorless needles crystallized; m.p. 208–210 °C (ref.[30,31] 203 °C; 210–211 °C). ^{1}H NMR: δ = 8.08 (s) ppm.

3,5-Dichloro-4-methoxybenzoic Acid (3c): Prepared, analogously as acid **3b**, from 4-bromo-2,6-dichloroanisole[32] (6.4·g, 25 mmol); colorless needles (from hexanes); m.p. 200–202 °C (ref.[33] 202–203 °C; ref.[34] no physical data); yield 5.03 g (91%). ^{1}H NMR: δ = 8.04 (s, 2 H), 3.98 (s, 3 H) ppm.

4-Bromo-2,6-dichloro-*N*,*N*-dimethylaniline: 2,6-Dichloro-*N*,*N*-dimethylaniline (9.5 g, 50 mmol) and bromine (2.5 mL, 8.0 g, 50 mmol) in chloroform were kept at 0 °C during 45 min. Upon direct distillation a colorless oil was collected; b.p. 78–80 °C/0.6 Torr; n_D^{20} = 1.5838; d_4^{20} = 1.691; yield 12.1 g (90%). ^{1}H NMR: δ = 7.39 (s, 2 H), 2.86 (s, 6 H) ppm. ^{13}C NMR: δ = 145.5, 135.8 (2 C), 131.4 (2 C), 117.0, 41.8 (2 C) ppm. $C_8H_8BrCl_2N$ (269.01): calcd. C 35.72, H 2.97; found C 35.69, H 3.03.

3,5-Dichloro-4-(dimethylamino)benzoic Acid (3e): 4-Bromo-2,6-dichloro-*N*,*N*-dimethylaniline (6.7 g, 25 mmol) was added to a solution of butyllithium (25 mmol) in hexanes (15 mL) and diethyl ether (35 mL) cooled in a dry ice/methanol bath. After 15 min at –75 °C, the reaction mixture was poured on an excess of freshly crushed dry ice, acidified with 2.0 M hydrochloric acid and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried and evaporated to give colorless needles after crystallization from ethyl acetate; m.p. 162–164 °C (ref.[35] m.p. 161–163 °C). ^{1}H NMR: δ = 7.97 (s, 2 H), 2.98 (s, 6 H) ppm.

Di-*tert*-butyl *N*-(4-Bromo-2,6-dichlorophenyl)iminodicarboxylate (Di-*tert*-butyl 4-Bromo-2,6-dichloroaniline-*N*,*N*-dicarboxylate): A solution of 4-bromo-2,6-dichloroaniline (24 g, 0.10 mol), di-*tert*-butyl dicarbonate (54 g, 0.24 mol) and 4-(dimethylamino)pyridine (1.3 g, 10 mmol) in tetrahydrofuran (0.20 L) was heated under reflux for 12 h. The reaction mixture was concentrated to half the volume, diluted with diethyl ether (0.15 L) and washed with a 2.0 M aqueous solution (0.10 L) of citric acid before being dried and the solvents evaporated. Crystallization from ethyl acetate gave colorless needles; m.p. 120–122 °C; yield 33.1 g (75%). ^{1}H NMR: δ = 7.53 (s, 2 H), 1.41 (s, 18 H) ppm. ^{13}C NMR: δ = 150.5 (2 C),

136.8 (2 C), 136.5, 132.6 (2 C), 122.9, 84.5 (2 C), 28.7 (6 C) ppm. $C_{16}H_{20}BrCl_2NO_4$ (441.15): calcd. C 43.56, H 4.50; found C 43.57, H 4.57.

***tert*-Butyl (4-Bromo-2,6-dichlorophenyl)carbamate:** The bis(carbamic acid) *tert*-butyl ester (22 g, 50 mmol) was treated with potassium carbonate (14 g, 0.10 mol) in refluxing methanol (50 mL) for 12 h. The reaction mixture was concentrated and partitioned between brine (50 mL) and diethyl ether (0.10 L). Evaporation of the organic layer gave colorless needles; m.p. 104–106 °C (from ethyl acetate); yield 16.7 g (98%). ^{1}H NMR: δ = 7.52 (s, 2 H), 1.49 (s, 9 H) ppm. ^{13}C NMR: δ = 152.4, 134.5 (2 C), 131.1 (2 C), 120.0 (2 C), 81.5, 27.9 (3 C) ppm. $C_{11}H_{12}BrCl_2NO_2$ (341.06): calcd. C 38.74, H 3.55; found C 38.73, H 3.56.

4-(*tert*-Butoxycarboxamido)-3,5-dichlorobenzoic Acid (3f): *tert*-Butyl (4-bromo-2,6-di-chlorophenyl)carbamate (8.5 g, 25 mmol) was added to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (20 mL) in a dry ice/methanol bath. After 15 min at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. At +25 °C, it was acidified with a 2.0 M aqueous solution (20 mL) of citric acid and extracted with ethyl acetate (3 × 25 mL). Upon concentration and cooling, colorless needles were obtained; m.p. 153–155 °C (from ethyl acetate); yield 6.88 g (90%). ^{1}H NMR: δ = 8.06 (s, 2 H), 6.59 (s, 1 H), 1.51 (s, 9 H) ppm. ^{13}C NMR: δ = 166.0, 154.1, 139.1 (2 C), 136.1, 132.2 (2 C), 130.9, 81.7, 29.2 (3 C) ppm. $C_{12}H_{13}Cl_2NO_4$ (306.15): calcd. C 47.07, H 4.28; found C 47.02, H 4.27.

3,5-Dichloro-4-methylbenzoic Acid (3g): At –75 °C, 2,6-dichloro-4-iodotoluene (7.2 g, 25 mmol; see the following paragraph) was added to a solution of isopropylmagnesium chloride (25 mmol) in tetrahydrofuran (35 mL). After 45 min in a dry ice/methanol bath, the reaction mixture was poured onto freshly crushed dry ice and, at +25 °C, acidified with a 2.0 M ethereal solution (15 mL) of hydrogen chloride (30 mmol) before being evaporated. Crystallization from hexanes gave colorless needles; m.p. 187–189 °C (ref.[36] m.p. 188 °C); yield 2.83 g (92%). ^{1}H NMR: δ = 8.00 (s, 2 H), 2.54 (s, 3 H) ppm.

2,6-Dichloro-4-iodotoluene: Diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and 1,3-dichloro-5-iodobenzene (14 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (70 mL) kept in a dry ice/methanol bath. After 2 h at –75°, the reaction mixture was poured into a precooled solution of dimethyl sulfate (7.0 mL, 7.5 g, 60 mmol) in tetrahydrofuran (50 mL). The reaction mixture was concentrated, diluted with diethyl ether (0.10 L), washed with a 2.0 M solution (20 mL) of hydrochloric acid and dried. Evaporation afforded colorless needles; m.p. 31–33 °C (from hexanes); yield 12.3 g (86%). ^{1}H NMR: δ = 7.61 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR: δ = 135.9 (2 C), 134.2, 129.1 (2 C), 89.2, 17.2 ppm. $C_7H_5Cl_2I$ (286.92): calcd. C 29.30, H 1.76; found C 29.33, H 1.82.

3,5-Dichloro-4-ethylbenzoic Acid (3h): Prepared, analogously as 3,5-dichloro-4-methylbenzoic acid (**3g**), from (1,3-dichloro-2-ethyl-4-iodobenzene (see below; 4.5 g, 15 mmol) and isopropylmagnesium chloride (15 mmol); colorless needles; m.p. 125–127 °C (from hexanes); yield 2.96 g (90%). ^{1}H NMR: δ = 7.93 (s, 2 H), 3.06 (q, J = 8.0 Hz, 2 H), 1.22 (t, J = 7.7 Hz, 3 H) ppm. ^{13}C NMR: δ = 169.3, 146.3, 135.8 (2 C), 130.6, 128.4 (2 C), 26.7, 11.8 ppm. $C_9H_8Cl_2O_2$ (219.07): calcd. C 49.35, H 3.68; found C 49.02, H 3.99.

1,3-Dichloro-2-ethyl-5-iodobenzene: Prepared, analogously as 2,6-dichloro-4-iodotoluene, using diethyl sulfate (6.6 mL, 7.8 g, 60 mmol) instead of dimethyl sulfate. Crystallization from pentanes gave colorless needles; m.p. 27–29 °C; yield 7.22 g (48%). ^{1}H NMR: δ = 7.80 (s, 2 H), 2.95 (q, J = 7.5 Hz, 2 H), 1.16 (t, J = 7.7 Hz, 3 H) ppm. ^{13}C NMR: δ = 141.8 (2 C), 138.0, 133.1 (2 C), 94.9, 51.4, 26.3 ppm.

3. Metalation and Carboxylation of 2-Substituted 1,3-Dichlorobenzenes

1,3-Dichloro-2-fluorobenzene (1a): 1,3-Dichloro-2-fluorobenzene (4.1 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (20 mL) and tetrahydrofuran (30 mL) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. At +25 °C, the reaction mixture was acidified to pH 1 with 2.0 M hydrochloric acid (50 mL) and extracted with ethyl acetate (3 × 25 mL). One tenth of the organic solution was treated with an ethereal solution of diazomethane until the yellow color persisted. According to gas chromatographic analysis (30 m, DB-1, 180 °C, 30 m, DB-Wax, 180 °C; tridecane as internal calibrated standard), the raw material was composed of 3-chloro-2-fluorobenzoic acid[37] (71%) and 2,4-dichloro-3-fluorobenzoic acid (**2a**; 18%). When lithium 2,2,6,6-tetramethylpiperidide was used as the base under otherwise unchanged reaction conditions, **2,4-dichloro-3-fluorobenzoic acid** (**2a**) was formed in a crude yield of 92%. Recrystallization from hexanes gave colorless needles; m.p. 138–140 °C; yield 4.60 g (88%). ^{1}H NMR: δ = 7.83 (dd, J = 8.3, 1.6 Hz, 1 H), 7.44 (dd, J = 8.6, 1.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.9 (d, J = 3 Hz), 156.2 (d, J = 247 Hz), 132.7 (m, 2 C), 130.4 (s), 128.8 (d, J = 5 Hz), 126.7 (d, J = 19 Hz) ppm. $C_7H_3Cl_2FO_2$ (209.00): calcd. C 40.23, H 1.45; found C 40.16, H 1.38.

1,2,3-Trichlorobenzene (1b): 1,2,3-Trichlorobenzene (4.5 g, 25 mmol) in tetrahydrofuran (10 mL) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (15 mL) and tetrahydrofuran (35 mL) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the mixture was poured on freshly crushed dry ice. The reaction mixture was acidified with a 2.0 M hydrochloric acid (25 mL). After extraction with ethyl acetate (3 × 25 mL) and filtration, one tenth of the organic solution was treated with diazomethane. According to gas chromatography (30 m, DB-Wax, 200 °C; 30 m, DB-1, 200 °C; pentadecane as the internal calibrated standard), the raw material contained 2,6-dichlorobenzoic acid[1] (67%) and 2,3-dichlorobenzoic acid[26] (5.7%), 2,3,4-trichlorobenzoic acid[38] (**2b**; 13%) and 3,4,5-trichlorobenzoic acid[30] (see Section 2; **3b**; 0.5%). When the metalation was performed with lithium 2,2,6,6-tetramethylpiperidide (25 mmol), the acid **2b** was obtained in 90% yield; colorless needles; m.p. 185–187 °C (ref.[38] m.p. 186–187 °C). ^{1}H NMR: δ = 7.84 (d, J = 8.5 Hz, 1 H), 7.50 (d, J = 8.5 Hz, 1 H) ppm.

2,6-Dichloroanisole (1c): 2,6-Dichloroanisole (4.4 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (30 mL) and tetrahydrofuran (20 mL) at –75 °C. After 45 min at this temperature, the reaction mixture was poured onto freshly crushed dry ice. At +25 °C, it was acidified with 2.0 M hydrochloric acid (25 mL). After extraction with ethyl acetate (3 × 25 mL), one tenth of the organic solution was treated with diazomethane. According to gas chromatography (30 m, DB-Wax, 200 °C; 30 m, DB-1, 200 °C; pentadecane as the internal calibrated standard), the raw material contained 2,4-dichloro-3-methoxybenzoic acid (**2c**) and 3,5-dichloro-4-methoxybenzoic acid[33] (see Section 2; **3c**) in the proportion of 97:3; yield 5.1 g (93%). Crystallization from hexanes afforded **2,4-dichloro-3-methoxybenzoic acid (2c)** as colorless needles; m.p. 163–164 °C (ref.[39] m.p. 163 °C); yield 4.7 g (85%). ^{1}H NMR: δ = 7.72 (d, J = 7.9 Hz, 1 H), 7.38 (d, J = 7.9 Hz, 1 H), 3.94 (s, 3 H) ppm. When the metalation was carried out with lith-

ium 2,2,6,6-tetramethylpiperidide under otherwise identical conditions, the ratio of acids **2c** and **3c** exceeded 99:1; yield 5.01 g (81%).

(2,6-Dichlorophenoxy)triethylsilane (1d): (2,6-Dichlorophenoxy)triethylsilane (5.0 mL, 6.9 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (19 mL) and tetrahydrofuran (30 mL) cooled to –75 °C. After 45 min at that temperature, the reaction mixture was poured onto freshly crushed dry ice. At +25 °C, it was acidified with 2.0 M hydrochloric acid (20 mL) and extracted with ethyl acetate (3 × 25 mL). One tenth of the organic solution was treated with diazomethane until the yellow color persisted. According to gas chromatography (30 m, DB-Wax, 270 °C; 30 m, DB-1, 280 °C, standard: pentadecane), the raw material contained 2,4-dichloro-3-hydroxybenzoic acid[33] (**2d**) and 3,5-dichloro-4-hydroxybenzoic acid[40–42] (**3d**) in a ratio of 91:9; yield 4.45 g (86%). Crystallization of the crude material from ethyl acetate afforded pure **2,4-dichloro-3-hydroxybenzoic acid**[33] (**2d**); m.p. 210–212 °C (ref.[33] m.p. 211–212 °C); yield 3.62 g (70%). ^{1}H NMR: δ = 7.58 (d, J = 8.5 Hz, 1 H), 7.38 (d, J = 8.6 Hz, 1 H) ppm. When the metalation was accomplished with lithium 2,2,6,6-tetramethylpiperidide (25 mmol), the ratio of acids **2d** and **3d** exceeded 99:1; yield 3.83 g (58%).

2,6-Dichloro-*N*,*N*-dimethylaniline (1e): 2,6-Dichloro-*N*,*N*-dimethylaniline (4.8 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (20 mL) and tetrahydrofuran (30 mL) kept in a dry ice/methanol bath. After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice was added and, when it had reached +25 °C, acidified with 2.0 M hydrochloric acid (25 mL) and extracted with ethyl acetate (3 × 25 mL). One tenth of the combined organic layers was treated with ethereal diazomethane. According to gas chromatography (30 m, DB-Wax, 250 °C; 30 m, DB-1, 250 °C; pentadecane as the internal calibrated standard), the raw material was composed of 2,4-dichloro-3-(dimethylamino)benzoic acid (**2e**) and 3,5-dichloro-4-(dimethylamino)benzoic acid (see Section 2; **3e**) in a 80:20 ratio; yield 3.63 g (62%). When lithium 2,2,6,6-tetramethylpiperidide (25 mmol) was used as the metalating reagent, **3,5-dichloro-4-(dimethylamino)benzoic acid** (**3e**) was obtained exclusively; yield 2.98 g (51%); m.p. 97–99 °C (dec.). –^{1}H NMR: δ = 7.55 (d, J = 8.3 Hz, 1 H), 7.46 (d, J = 8.3 Hz, 1 H), 2.89 (s, 6 H) ppm. ^{13}C NMR: δ = 167.7, 157.7, 149.0, 139.7, 134.5, 130.4, 128.8, 43.0 (2 C) ppm. $C_9H_9Cl_2NO_2$ (234.11): calcd. C 46.17, H 3.88; found C 46.06, H 3.89.

***tert*-Butyl (2,6-dichlorophenyl)carbamate (1f):** Potassium *tert*-butoxide (5.6 g, 50 mmol) and *tert*-butyl (2,6-dichlorophenyl)carbamate (6.5 g, 25 mmol) were consecutively added to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (70 mL) kept in a dry ice/methanol bath. After 12 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. At +25 °C, the reaction mixture was acidified with a 2.0 M aqueous solution (25 mL) of citric acid and extracted with ethyl acetate (3 × 25 mL) before being dried and the solvents evaporated. According to ^{1}H NMR (using dioxane as an internal standard for quantification), the white residue contained 2,4-dichloro-3-(*tert*-butoxycarboxamido)benzoic acid (**2f**) and 3,5-dichloro-4-(*tert*-butoxycarboxamido)-benzoic acid (**3f**) in a 95:5 ratio; yield 4.28 g (56%). Pure **3-(*tert*-butoxycarboxamido)-2,4-dichlorobenzoic acid** (**2f**) was obtained by crystallization from ethyl acetate; colorless needles; m.p. 147–149 °C; yield 3.52 g (46%). ^{1}H NMR: δ = 7.94 (d, J = 8.6 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR: δ = 166.2, 149.0, 137.2, 136.3, 134.1, 131.0, 129.9, 126.9, 83.0, 30.0 (3 C) ppm. $C_{12}H_{13}Cl_2NO_4$ (306.15): calcd. C 47.07, H 4.28; found C 46.77, H 4.06.

2,6-Dichlorotoluene (1g): 2,6-Dichlorotoluene (3.1 mL, 4.0 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (20 mL) and tetrahydrofuran (30 mL) kept in a dry ice/methanol bath. After 45 min at –75 °C, the mixture was poured on dry ice before being, at +25 °C, acidified with 2.0 M hydrochloric acid (25 mL) and extracted with ethyl acetate (3 × 25 mL). One tenth of the organic solution was treated with ethereal diazomethane. According to gas chromatographic analysis (30 m, DB-Wax, 200 °C; 30 m, DB-1, 200 °C; tridecane as the internal calibrated standard), the crude product mixture contained (2,6-dichlorophenyl)acetic acid,[43,44] 2,4-dichloro-3-methylbenzoic acid[45] (**2g**) and 3,5-dichloro-4-methylbenzoic acid (**3g**; see Section 2) in a 80:16:4 ratio; yield 4.56 g (89%). $C_8H_6Cl_2O_2$ (205.01): calcd. C 46.87, H 2.95; found C 46.91; H 3.10. When lithium 2,2,6,6-tetramethylpiperidide (25 mmol) was used as the metalating reagent, (2,6-dichlorophenyl)acetic acid and acid **2g** were obtained in a 75:25 ratio and in a yield of 3.49 g (68%), whereas lithium diisopropylamide (25 mmol) gave only **(2,6-dichlorophenyl)acetic acid**; colorless needles (from hexanes); m.p. 154–156 °C (ref.[43,44] m.p. 156–157 °C). –^{1}H NMR: δ = 7.33 (d, J = 8.0 Hz, 2 H), 7.18 (t, J = 8.3 Hz, 1 H), 4.08 (s, 2 H) ppm.

1,3-Dichloro-2-ethylbenzene (1h): At –75 °C, 1,3-dichloro-2-ethylbenzene (3.5 mL, 4.4 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (20 mL) and tetrahydrofuran (30 mL) After 45 min at –75 °C, the mixture was poured onto an excess of freshly crushed dry ice. At +25 °C, it was acidified with 2.0 M hydrochloric acid and extracted with ethyl acetate (3 × 25 mL). One tenth of the organic phase was treated with ethereal diazomethane. According to gas chromatography (30 m, DB-Wax, 200 °C; 30 m, DB-1, 200 °C, tridecane as the internal calibrated standard), the raw material contained 2,4-dichloro-3-ethylbenzoic acid (**2h**) and 3,5-dichloro-4-ethylbenzoic acid (see Section 2; **3h**) in a 74:26 ratio; yield 4.51 g (77%). Lithium 2,2,6,6-tetramethylpiperidide (25 mmol) as the base produced exclusively **2,4-dichloro-3-ethylbenzoic acid** (**2h**); yield 1.70 g (31%); m.p. 98–100 °C (from hexanes). ^{1}H NMR: δ = 7.72 (d, J = 8.3 Hz, 1 H), 7.37 (d, J = 8.3 Hz, 1 H), 3.06 (q, J = 7.4 Hz, 2 H), 1.20 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 167.4, 142.5, 138.9, 134.7, 133.9, 130.5, 129.7, 26.3, 13.5 ppm. $C_9H_8Cl_2O_2$ (219.04): calcd. C 49.35, H 3.68; found C 49.27, H 3.60.

2,6-Dichlorobenzotrifluoride (1i): 2,6-Dichloro-4-(trifluoromethyl)-benzene (5.4 g, 25 mmol) in tetrahydrofuran (30 mL) and cyclohexane (20 mL) was treated consecutively with *sec*-butyllithium (25 mmol; 2 h at –75 °C) and dry ice. A small portion of the crude reaction mixture (equivalent to roughly 1.0 mmol) was acidified to pH 1, esterified with ethereal diazomethane and hydrogenolytically dechlorinated.[46,47] Gas chromatographic analysis (30 m, DB-Wax, 150 °C; 30 m, DB-30, 130 °C; tridecane as the internal standard′′) revealed the presence of methyl 2-, 3- and 4-(trifluoromethyl)benzoate in an 8:3:1 ratio corresponding to yields of 49%, 19% and 6% (in total 74%). When the bulk of the mixture was worked up by neutralization and extraction, the main product 3-chloro-2-(trifluoromethyl)benzoic acid was obtained after crystallization from an ethanol/hexanes mixture as colorless needles; m.p. 119–121 °C; yield 1.74 g (31%). The second abundant component, the 2,4-dichloro-3-(trifluoromethyl)benzoic acid (**2i**), was identified in the mother liquors by ^{1}H NMR spectroscopy. It was independently prepared from 2,6-dichloro-4-(trifluoromethyl)benzene (25 mmol) by consecutive treatment with LITMP and dry ice; colorless platelets; m.p. 136–138 °C; yield 4.60 g (71%). All further details can be found in a previous report.[48]

Acknowledgments

This work was financially supported by the Swiss National Science Foundation, Bern (grant 20-100'336-02) and the Federal Office for Education and Science, Bern (grant C02.0060 linked to the COST-D24 project WG0006-02).

[1] C. Heiss, E. Marzi, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 4625–4629.
[2] C. Heiss, F. Cottet, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 5236–5241.
[3] J. Gorecka, C. Heiss, R. Scopelliti, M. Schlosser, *Org. Lett.* **2004**, *6*, 4591–4593.
[4] D. L. Nguyên, M. Schlosser, *Helv. Chim. Acta* **1977**, *60*, 2085–2088.
[5] S. Takagishi, M. Schlosser, *Synlett* **1991**, 119–121.
[6] M. Schlosser, C. Heiss, *Eur. J. Org. Chem.* **2005**, 5242–5247.
[7] M. Schlosser, F. Cottet, C. Heiss, O. Lefebvre, M. Marull, E. Masson, R. Scopelliti, *Eur. J. Org. Chem.* **2006**, 729–734.
[8] M. Schlosser, C. Heiss, F. Leroux, *Eur. J. Org. Chem.* **2006**, 735–737.
[9] M. Schlosser, J. H. Choi, S. Takagishi, *Tetrahedron* **1990**, *46*, 5633–5648.
[10] E. Baston, Q. Wang, M. Schlosser, *Tetrahedron Lett.* **2000**, *41*, 667–670.
[11] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
[12] D. Damrauer, S. R. Kass, C. H. DePuy, *Organometallics* **1988**, *7*, 637–640.
[13] D. M. Wetzel, J. I. Brauman, *J. Am. Chem. Soc.* **1988**, *110*, 8333–8336.
[14] R. Radinov, C. Chanev, M. Haimova, *J. Org. Chem.* **1991**, *56*, 4793–4796.
[15] E. Marzi, Doctoral Dissertation, EPF Lausanne, **2001**, pp. 49–50.
[16] I. F. Tupytsin, N. K. Seminova, *Tr., Gos. Inst. Prikl. Khim.* **1962**, *49*, 120–132 [*Chem. Abstr.* **1964**, *60*, 6721].
[17] J. A. Zoltewicz, C. L. Smith, *J. Am. Chem. Soc.* **1967**, *89*, 3358–3359.
[18] J. A. Zoltewicz, G. Grahe, C. L. Smith, *J. Am. Chem. Soc.* **1969**, *91*, 5501–5505.
[19] I. F. Tupitsyn, N. N. Zatspina, A. V. Kirova, Y. L. Kaminskii, A. G. Ivanenko, *Reakts. Sposobnost Org. Soedin* **1973**, *10*, 143–162 [*Chem. Abstr.* **1973**, *79*, 114928].
[20] C. Bobbio, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 4533–4536.
[21] M. Masson, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 4401–4405.
[22] F. Leroux, O. Lefebvre, M. Schlosser, *Eur. J. Org. Chem.* **2006**, 3147–3151.
[23] M. J. Strauss, L. J. Andrews, R. M. Keefer, *J. Am. Chem. Soc.* **1968**, *90*, 3473–3478.
[24] P. P. Alikhanov, K. I. Sakodynskii, G. N. Kuznetsova, *Zh. Anal. Khim.* **1987**, *42*, 712–717 [*Chem. Abstr.* **1987**, *107*, 190045].
[25] R. Bolton, J. P. B. Sandall, *J. Chem. Soc., Perkin Trans. 2* **1977**, 278–280.
[26] E. Hope, G. C. Riley, *J. Chem. Soc.* **1923**, *123*, 2470–2480, specifically p. 2478–2479.
[27] C. Heiss, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 447–451.
[28] M. Schlosser, *Angew. Chem.* **2005**, *117*, 380–398; *Angew. Chem. Int. Ed.* **2005**, *44*, 376–393, specifically p. 391 or p. 386, respectively.
[29] D. N. Kravtsov, B. A. Kvasov, T. S. Khazanova, E. I. Fedin, *J. Organomet. Chem.* **1973**, *61*, 207–218, specifically p. 216.
[30] H. Salkowski, *Justus Liebigs Ann. Chem.* **1872**, *163*, 1–64, specifically p. 27–33.
[31] C. van de Bunt, *Recl. Trav. Chim. Pays-Bas* **1929**, *48*, 121–146, specifically p. 132.
[32] J. J. Li, M. B. Norton, E. J. Reinhard, G. D. Anderson, S. A. Gregory, P. C. Isakson, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, K. Seibert, Y. Zhang, B. S. Zweifel, D. B. Reitz, *J. Med. Chem.* **1996**, *39*, 1846–1856.
[33] T. H. Durrans, *J. Chem. Soc.* **1923**, *123*, 1424–1429.
[34] H.-C. Huang, J. J. Li, D. J. Garland, T. S. Chamberlain, E. J. Reinhard, R. E. Manning, K. Seibert, C. M. Koboldt, S. A. Gregory, C. D. Anderson, A. W. Veenhuizen, Y. Zhang, W. E. Perkins, E. G. Burton, J. N. Cogburn, P. C. Isakson, D. B. Reitz, *J. Med. Chem.* **1996**, *39*, 253–266, specifically p. 265.
[35] J. E. Martinelli, M. Chaykovsky, *J. Org. Chem.* **1980**, *45*, 527–529.
[36] A. Claus, P. Böcher, *Justus Liebigs Ann. Chem.* **1891**, *265*, 351–363, specifically p. 361.
[37] F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1996**, *37*, 6551–6554.
[38] J. B. Cohen, H. D. Dakin, *J. Chem. Soc.* **1902**, *81*, 1324–1344, specifically p. 1328.
[39] A. Mooradian, T. J. Slouson, S. J. Marsala, *J. Am. Chem. Soc.* **1951**, *73*, 3470–3472.
[40] T. Zincke, *Justus Liebigs Ann. Chem.* **1891**, *261*, 208–254, specifically p. 254.
[41] D. S. Tarbell, J. W. Wilson, *J. Am. Chem. Soc.* **1942**, *64*, 1066–1070.
[42] D. S. Tarbell, J. W. Wilson, P. E. Fanta, *Org. Synth., Coll. Vol.* **1955**, *3*, 267–270.
[43] P. R. Austin, J. R. Johnson, *J. Am. Chem. Soc.* **1932**, *54*, 647–660, specifically p. 659.
[44] S. Holmquist, *Acta Chem. Scand.* **1955**, *9*, 1012–1012.
[45] I. P. Uvarova, L. P. Golod, A. V. Yazlovitskii, S. D. Rudenko, F. F. Shcherbina, A. A. Girgorev, *Zh. Prikl. Khim (Leningrad)* **1990**, *63*, 483–486 [*Chem. Abstr.* **1990**, *113*, 23289].
[46] F. Cottet, E. Castagnetti, M. Schlosser, *Synthesis* **2005**, 798–803.
[47] C. Bobbio, M. Schlosser, *J. Org. Chem.* **2005**, *70*, 3039–3045.
[48] E. Masson, E. Marzi, F. Cottet, C. Bobbio, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 4393–4400.

Received: April 24, 2006
Published Online: July 28, 2006

