Optional Site Selectivity in the Metalation of *o*- and *p*-Anisidine through Matching of Reagents with Neighboring Groups

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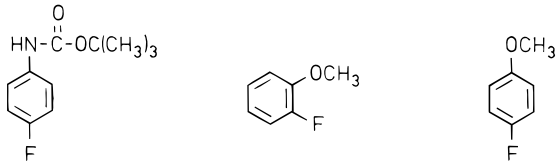
N-Protected *o*- and *p*-anisidines (2- and 4-methoxyanilines) undergo a hydrogen/metal exchange at the position adjacent to *either* the oxygen *or* nitrogen atom depending on what organometalic base is employed. These synthetically useful findings support previous views about neighboring group/reagent interactions.

In the late 1930s, pentylsodium,[1] phenyllithium,[2] and butyllithium[3] were found to bring about a hydrogen/metal interconversion ("metalation") at the position adjacent to the alkoxy moiety of anisole. The importance of this discovery can hardly be overestimated; it was one of the key events in the development of modern organic synthesis. For the first time, hope began to grow that electrophilic aromatic substitutions must not fatally lead to mixtures of regioisomeric products as characteristic of Friedel−Crafts-type reactions. The crucial and novel feature was the *ortho* selectivity of the exchange process. The subsequent replacement by a suitable electrophile would obviously not compromise the structural uniformity achieved at the crucial stage of metal introduction.

Later a host of other heterofunctional groups were found to exhibit the same *ortho* directing effect.[4] However, the origin of the neighboring group assistance has always remained a controversial issue. To simplify the discussion, one can contrast two schools of thought. Many researchers attribute the enhanced deprotonation rates in the vicinity of heterosubstituents to the electronegativity of the latter.[5] The resulting *inductive electron-withdrawal* being powerful only within short range, *ortho* are considerably more "acidified" than *meta*, not to speak of *para* positions. Others, arguing just in the opposite sense, drawing attention to the nonbonding ("lone pair") electrons with which heteroatoms happen to be endowed. Consequently, they can act as *electron-donor ligands* and coordinate metals, in particular lithium atoms.[6] In this way the organometallic reagent gets tied up with the substrate and the ensuing acid−base reaction can occur in an entropy-economic intracomplex mode if, and only if, the nearby *ortho* position is selected as the target.

At first sight, these two views do not appear to be reconcilable. However, as a careful analysis has revealed, the inductive and the coordinative effect are operating simultaneously, often even cooperatively.[7,8] Which factor is preponderant in a given case does not only depend on the nature of the neighboring group involved but also on the kind of reagent used. As a rule of thumb, weakly solvated organolithium compounds optimally exploit the coordinative capacities of a substituent, whereas *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) complexed butyllithium or organopotassium species preferentially deprotonate such positions where charge excess is most efficiently stabilized.[7]

This *mechanism-based matching of neighboring groups and reagents* has allowed us to metalate arenes carrying two different heterosubstituents with *optional site selectivities*.[7−10] For example, *N*-*tert*-butoxycarbonyl ("BOC") protected 4-fluoroaniline[8] selectively undergoes a hydrogen/metal exchange at the nitrogen adjacent position, with *tert*-butyllithium alone, but at the position next to the halogen, when its adduct with potassium *tert*-butoxide is applied as the organometallic base. Butyllithium in tetrahydrofuran deprotonates 2- and 4-fluoroanisole[9] exclusively at the oxygen adjacent position while the same reagent, when activated by PMDTA or potassium *tert*-butoxide, only attacks CH bonds in the immediate vicinity of the halogen.



The closer the two competing substituents resemble each other electronically, the more difficult it is to exploit individual differences by establishing optional site selectivity. Keeping this in mind, we decided to study the metalation of *N*-protected anisidines, arguably the toughest challenge of this type. Although the margins of experimental maneuvre are narrow indeed, we have been able to identify conditions which ensure good to excellent selectivities.

By consecutive treatment with butyllithium in the presence of potassium *tert*-butoxide (LIC-KOR) in tetra-

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(3) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109−112.

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(5) Young, S. D.; Coblens,K. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4887−4888.

(6) Morton, A. A.; Little, E. L.; Strong, W. O.; *J. Am. Chem. Soc.* **1943**, *65*, 1339−1346. Morton, A. A. *J. Am. Chem. Soc.* **1947**, *69*, 969−971.

(7) Schlosser, M. *Mod. Synth. Meth.* **1992**, *6*, 227−271, Scheffold, R., Ed. Schlosser, M.; Faigl, F.; Franzini, L.; Geneste, H.; Katsoulos, G.; Zhong, G.-f. *Pure Appl. Chem.* **1994**, *66*, 1423−1446.

(8) Takagishi, S.; Katsoulos, G.; Schlosser, M. *Synlett* **1992**, 360−362.

(9) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731−732.

(10) For another recent, still puzzling example of optional site selectivity, see: Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815−10816.

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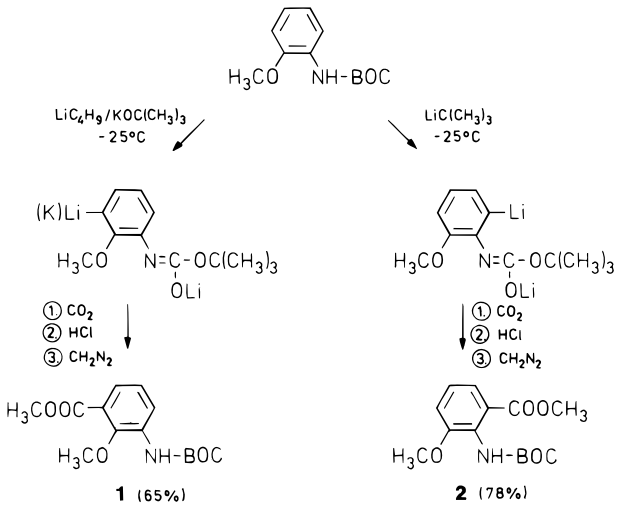
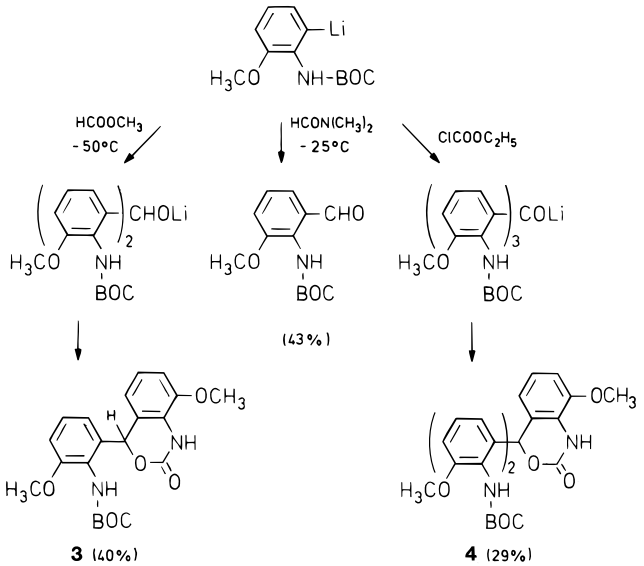
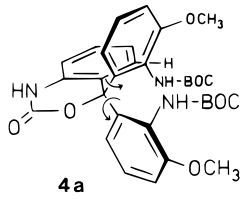
hydrofuran at −25 °C and dry ice, *N*-BOC-*o*-anisidine was smoothly converted into pure 3-[*tert*-butoxycarbonyl)-amino]-2-methoxybenzoic acid and, by reaction of the latter with diazomethane, into its methyl ester (**1**, 55%). The yield raised to 65% when an excess of the metalating reagent was employed. In contrast, metalation with *tert*-butyllithium in diethyl ether, again at −25 °C, followed by carboxylation gave exclusively the regioisomeric product 2-[*tert*-butoxycarbonyl)amino]-3-methoxybenzoic acid, isolated again as the methyl ester (**2**, 78%).



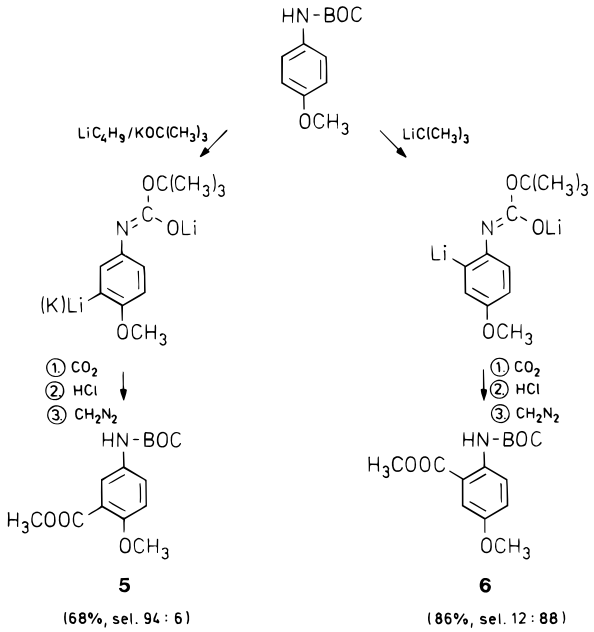
We have advertised the "2-fold reaction benchmark"[11] as a simple, although conclusive, test on the performance of a synthetic method. We have applied it to the anisidine case by treating the organolithium species carrying the metal next to the nitrogen atom with methyl formate and ethyl chloroformate. Rather than obtaining the expected di- and triarylcarbinols, we have isolated the oxazinone derivatives **3** (40%) and **4** (29%). The ring closure is obviously brought about by the intramolecular attack of the alcoholate function onto a *tert*-butoxycarbonyl moiety. The yield of the benzhydrol **3** was increased (to 50%), when methyl formate was replaced by *tert*-butyl *N*-(2-formyl-6-methoxyphenyl)carbamate, the latter having been prepared in 43% yield by the reaction between the organolithium intermediate and *N*,*N*-dimethylformamide.



As the inspection of molecular models has revealed, the rotation around the axes of the geminal aryl groups should be severely hindered (as illustrated by the perspective drawing **4a**). Actually, the NMR signals of their *tert*-butoxy and methoxy substituents appear pairwise at room temperature and become magnetically equivalent only around 75 °C. On the basis of the coalescence temperatures, a barrier of 17 kcal/mol, impeding the correlated[12] torsional motion, was calculated.



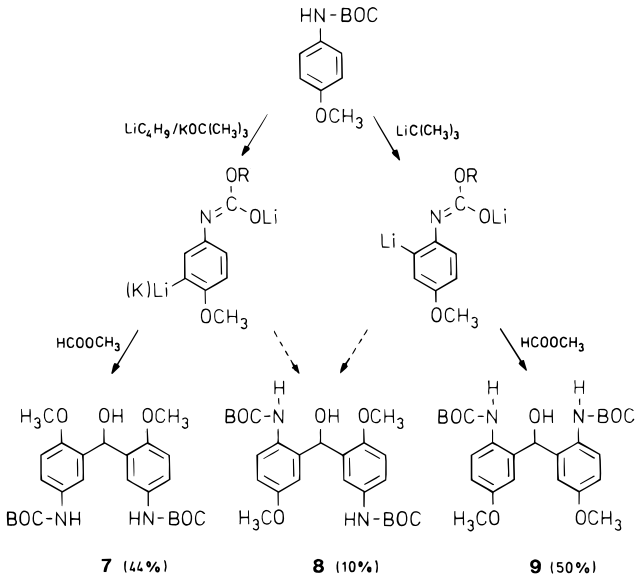
The site selection was less perfect with *N*-BOC-*p*-anisidine as the substrate. Metalation with the superbasic LIC-KOR reagent followed by carboxylation, neutralization, and treatment with diazomethane afforded 5-[(*tert*-butoxycarbonyl)amino]-2-methoxybenzoic acid methyl ester (**5**) and 2-[(*tert*-butoxycarbonyl)amino]-5-methoxybenzoic acid methyl ester (**6**) in a 94:6 ratio with 68% total yield, while metalation with *tert*-butyllithium produced the esters **5** and **6** as a 12:88 mixture and in 86% yield.



When in the latter reaction carbon dioxide was replaced by methyl formate as the electrophile, di-*tert*-butyl 2,2′-hydroxymethylenebis[(4-methoxyphenyl)carbamate] **9** resulted as the main product (50%). The structure of the unsymmetrical *N*-adjacent *O*′-adjacent isomer **8** was tentatively assigned to the minor component (10%) isolated from the same reaction mixture. No trace of the *O*,*O*′-adjacent isomer **7**, the sole product (44%) identified after metalation with LIC-KOR, was detected in this experiment.

A change of the protective group may improve or worsen the selectivity of the substitution reaction. *N*′-(4-Methoxyphenyl)-*N*,*N*-dimethylurea was found to be

(11) Schlosser, M.; Bossert, H. *Tetrahedron* **1991**, *47*, 6287−6292.
(12) Mislow, K. *Acc. Chem. Res.* **1976**, *9*, 26−33.



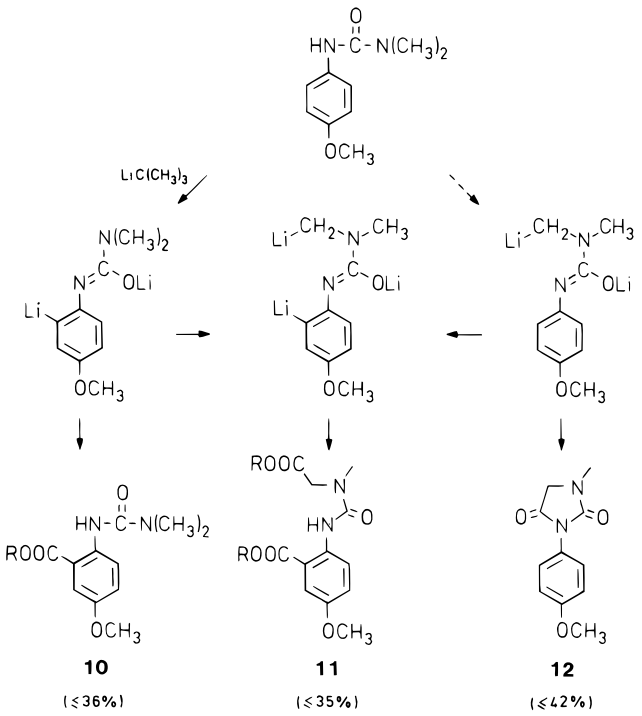
attacked by *tert*-butyllithium exclusively at the *N*-adjacent ring position but concomitantly also at a side chain methyl group.[13] Thus, after carboxylation, a mixture of 2-[[(*N*′,*N*′-dimethylamino)carbonyl]amino]-5-methoxybenzoic acid, isolated as the methyl ester **10** (RO = H_3CO; maximum yield 36%), dicarboxylic acid **11** (RO = HO; maximum yield 35%), and hydantoin **12** (maximum yield 42%) was obtained, the proportions varying with the reaction conditions. The ureido ester **10** could be selectively hydrolyzed in 5 M hydrochloric acid (24 h, 100 °C) to give 2-amino-5-methoxybenzoic acid (5-methoxyanthranilic acid; 89%). Remarkably, with *N*,*N*-diethyl-*N*′-(4-methoxyphenyl)urea as the substrate, metalation at the side chain no longer took place, but *N*- and *O*-adjacent ring positions were simultaneously lithiated.

In conclusion, we find our first-order principles[7,8] confirmed. Polar, in particular superbasic mixed-metal reagents, preferentially attack the inductively activated aromatic position next to the most electronegative heteroatom while organolithium reagents in need of coordination operate in the immediate vicinity of the most powerful electron-donor substituent.

Experimental Section

General. For practical routine and technical details, see other recent articles[14] published by this laboratory. ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at 400 MHz, the samples having been dissolved in deuteriochloroform.

(1) Reactions Involving *N*-BOC Protected *o*-Anisidine. Methyl 3-[(*tert*-Butoxycarbonyl)amino]-2-methoxybenzoate (1). At −75 °C, *tert*-butyl (2-methoxyphenyl)carbamate[15] (5.6 g, 25 mmol) and a 1.5 M solution of butyllithium (50 mmol) in hexane (33 mL) were added to potassium *tert*-butoxide (5.6 g, 50 mmol) in tetrahydrofuran (60 mL). After



20 h of stirring at −25 °C, the mixture was poured on an excess of freshly crushed dry ice. After evaporation of the solvents, the residue was taken up in water (0.10 L). The aqueous phase was washed with diethyl ether (2 × 50 mL), acidified to pH 5, and extracted with diethyl ether (3 × 50 mL) and dichloromethane (3 × 50 mL). The combined organic layers were dried, concentrated, and treated with an ethereal solution of diazomethane until the yellow color persisted. Distillation afforded a yellowish oil: mp −7 to −3 °C (from dichloromethane/hexane 1:2); bp 172−175 °C/1 mmHg; yield 55%; ^{1}H-NMR δ 8.30 (1 H, d, broad, J = 8.0), 7.47 (1 H, dd, J = 7.8, 1.5), 7.16 (1 H, s, broad), 7.12 (1 H, t, J = 8.1), 3.92 (3 H, s), 3.87 (3 H, s), 1.53 (9 H, s); MS m/z 281 (11, M^+), 225 (66), 181 (100). Anal. Calcd for $C_{14}H_{19}NO_5$ (281.31): C, 59.78; H, 6.81. Found: C, 59.67; H, 6.83.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-methoxybenzoate (2). At −75 °C, a 1.0 M solution of *tert*-butyllithium (50 mmol) in pentane (50 mL) is added to *tert*-butyl (2-methoxyphenyl)carbamate[15] (5.6 g, 25 mmol) in diethyl ether (50 mL). The mixture was stirred 20 h at −25 °C before being poured on an excess of freshly crushed dry ice. Water (0.20 L) was added, and the aqueous layer was washed with diethyl ether (2 × 50 mL) before being acidified to pH 5. After extraction with diethyl ether (3 × 50 mL) and dichloromethane (2 × 50 mL), the organic layers were combined, dried, and evaporated to dryness. Upon treatment of the residue with an ethereal solution of diazomethane, pale yellow prisms were obtained: mp 121−123 °C (from dichloromethane/hexane 1:3); yield 78%; ^{1}H-NMR δ 7.38 (1 H, dd, J = 7.9, 1.4), 7.18 (1 H, s, broad), 7.11 (1 H, t, J = 8.0), 7.02 (1 H, dd, J = 8.2, 1.4), 3.88 (3 H, s), 3.86 (3 H, s), 1.49 (9 H, s); MS m/z 281 (7, M^+), 181 (100); 166 (26). Anal. Calcd for $C_{14}H_{19}NO_5$ (281.31): C, 59.78; H, 6.81. Found: C, 59.80; H, 6.73.

***tert*-Butyl (2-Formyl-6-methoxyphenyl)carbamate.** In the same way as described in the preceding paragraph, *tert*-butyl (2-methoxyphenyl)carbamate[15] (5.6 g, 25 mmol) was treated with *tert*-butyllithium and, after 20 h at −25 °C, with *N*,*N*-dimethylformamide (2.0 mL, 2.1 g, 26 mmol). The mixture was extracted with a 15% aqueous solution (2 × 0.10 L) of sodium hydrogen sulfite. Sodium hydroxide was added to the combined aqueous layers until the basicity approximated pH 10. Upon extraction with diethyl ether (3 × 50 mL), drying and evaporation, pale yellow platelets were obtained: mp 106−108 °C (from methanol); yield 43%; ^{1}H-NMR δ 10.02 (1 H, s), 7.47 (1 H, dd, J = 7.9, 1.3), 7.22 (1 H, t, J = 7.9), 7.08 (1 H, dd, J = 8.1, 1.3), 6.93 (1 H, s, broad), 3.90 (3 H, s), 1.50 (9 H, s); MS m/z 251 (9, M^+), 178 (27), 151 (92), 123 (100). Anal.

(13) For analogies see, *e.g.*: Peterson, D. J.; Hays, H. R. *J. Org. Chem.* **1965**, *30*, 1939−1942. Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* **1984**, *25*, 1353−1356. Fraser, R. R.; Grindley, T. B. *Can. J. Chem.* **1975**, *53*, 2465−-2472. Seebach, D.; Wykpiel, W.; Lubosch, W.; Kalinowski, H. O. *Helv. Chim. Acta* **1978**, *61*, 3100−3102. Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1989**, *30*, 1197−1200. Schakel, M.; Aarnts, M. P.; Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 305−306. Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708−9710.

(14) Schlosser, M.; Keller, H. *Liebigs Ann. Chem.* **1995**, 1587−1589. Desponds, O.; Schlosser, M. *J. Organomet. Chem.* **1996**, *507*, 257−261. Shi, G.-q.; Wang, Q.; Schlosser, M. *Tetrahedron* **1996**, *52*, 4403−4410.

(15) Iwao, M. *Heterocycles* **1994**, *38*, 45−50; *Chem. Abstr.* **1994**, *120*, 244532n.

Calcd for $C_{13}H_{17}NO_4$ (251.28): C, 62.14; H, 6.82. Found: C, 62.33; H, 7.08.

4-[2-[(*tert*-Butoxycarbonyl)amino]-3-methoxyphenyl]-1,4-dihydro-8-methoxy-2*H*-3,1-benzoxazin-2-one (3). As described for the preparation of benzoate **2**, *tert*-butyl (2-methoxyphenyl)carbamate[15] (5.6 g, 25 mmol) was treated with *tert*-butyllithium. At −50 °C, methyl formate (0.74 mL, 0.72 g, 12 mmol) was added dropwise, in the course of 10 min. After 6 h at −50 °C, the mixture was poured into water (0.10 L). Extraction with diethyl ether (2 × 75 mL) and dichloromethane (50 mL), evaporation, and chromatography on a silica gel support using a 2:3 (v/v) mixture of ethyl acetate and hexane as the eluent afforded pale yellow platelets; mp 175−177 °C dec (from dichloromethane/hexane 1:3); yield 40%; ^{1}H-NMR δ 7.42 (1 H, s), 7.16 (1 H, t, J = 8.1), 6.96 (1 H, t, J = 8.0), 6.92 (1 H, dd, J = 8.1, 1.2), 6.84 (1 H, d, J = 8.0), 6.72 (1 H, s), 6.71 (1 H, d, broad), 6.64 (1 H, d, broad), 6.17 (1 H, s, broad), 3.90 (3 H, s), 3.86 (3 H, s), 1.45 (9 H, s); MS *m*/*z* 401 (3, M^+), 3.45 (100), 301 (59), 240 (43). Anal. Calcd for $C_{21}H_{24}N_2O_6$ (400.43): C, 62.99; H, 6.04. Found: C, 63.11; H, 6.19. When methyl formate had been replaced by *tert*-butyl (2-formyl-6-methoxyphenyl)carbamate, the heterocyclic product **3** was isolated in 50% yield.

Bis-4,4-[2-[(*tert*-butoxycarbonyl)amino]-3-methoxyphenyl]-1,4-dihydro-8-methoxy-2*H*-3,1-benzoxazin-2-one (4). An analogous reaction, employing ethyl chloroformate (0.78 mL, 8.1 mmol), gave pale yellow platelets: mp 196−200 °C dec (from dichloromethane/hexane 1:3); yield 29%; ^{1}H-NMR ($CDCl_3$; 25 °C) δ 7.40 (1 H, s), 7.18 (1 H, s, broad), 7.06 (1 H, t, J = 8.1), 6.95 (1 H, t, J = 8.0), 6.9 (2 H, m), 6.87 (1 H, d, J = 8.1), 6.72 (1 H, s, broad), 6.39 (1 H, s, broad), 6.22 (1 H, s, broad), 3.89 (3 H, s), 3.84 (3 H, s), 3.80 (3 H, s), 1.24 (9 H, s), 1.18 (9 H, s); ^{1}H-NMR (D_3CSOCD_3; 25 °C) δ 7.21 (1 H, s, broad), 7.1 (4 H, m), 6.90 (1 H, t, J = 8.0), 6.76 (1 H, s, broad), 6.45 (1 H, s, broad), 6.07 (1 H, s, broad), 3.82 (3 H, s), 3.75 (3 H, s), 3.72 (3 H, s), 1.20 (9 H, s), 1.13 (9 H, s); ^{1}H-NMR (D_3CSOCD_3; 100 °C) δ 7.1 (5 H, m), 6.92 (1 H, t, J = 7.9), 6.47 (1 H, d, J = 7.8), 6.38 (2 H, s, broad), 3.87 (3 H, s), 3.78 (6 H, s), 1.23 (18 H, s) MS *m*/*z* 622 (22, M^+), 580 (8), 522 (12), 461 (41), 405 (21), 79 (100). Anal. Calcd for $C_{33}H_{39}N_3O_9$ (621.69): C, 63.76; H, 6.32. Found: C, 63.96; H, 6.34. Coalescence of the signals at 3.75 and 3.72 (both 3 H) occurred at 326.0 K, that of the signals at 1.20 and 1.13 (both 9 H), at 337.5 K. Applying the standard equations,[16] gave an activation barrier of 17.1 (± 0.1) kcal/mol.

(2) Reactions Involving *N*-BOC-Protected *p*-Anisidine. Methyl 5-[(*tert*-Butoxycarbonyl)amino]-2-methoxybenzoate (5). The metalation of *tert*-butyl (4-methoxyphenyl)-carbamate[17] (5.6 g, 25 mmol) was accomplished with butyllithium in the presence of potassium *tert*-butoxide, the intermediate was intercepted with carbon dioxide, and the mixture was worked up as described for the preparation of isomer **1** (see section 1). After treatment of the residue with diazomethane, colorless needles were obtained: mp 111.0−112.5 °C (from dichloromethane/hexane 1:3); yield 68%. According to gas chromatography (30 m, DB-1701, 220 °C), **5** was contaminated by its regioisomer **6** in the ratio 94:6: ^{1}H-NMR δ 7.74 (1 H, d, J = 2.7), 7.56 (1 H, d, broad), 6.92 (1 H, d, J = 9.0), 6.46 (1 H, s, broad), 3.88 (6 H, s), 1.51 (9 H, s); MS *m*/*z* 281 (13, M^+), 225 (100), 181 (27). Anal. Calcd for $C_{14}H_{19}NO_5$ (281.31): C, 59.78, H, 6.81. Found: C, 59.79, H, 6.79.

Di-(*tert*-butyl) 3,3′-Hydroxymethylenebis[(4-methoxyphenyl)carbamate] (7). In an analogous reaction as the one described in the preceding paragraph, carbon dioxide was replaced by methyl formate (0.74 mL, 0.72 g, 12 mmol). After neutralization, the product was extracted with diethyl ether (3 × 50 mL), absorbed on silica gel (25 mL), and eluted from a column filled with more silica (500 mL) using a 1:4 (v/v) mixture of ethyl acetate and hexane. White platelets were obtained: mp 200−203 °C dec (from dichloromethane/hexane 1:3); yield 44%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.52 (2 H, s, broad), 6.88 (2 H, d, J = 2.4), 6.82 (2 H, d, J = 8.8), 6.33 (2 H, s, broad), 6.28 (1 H, d, J = 4.0), 3.79 (6 H, s), 3.43 (1 H, d, J = 4.4), 1.48 (18 H, s); MS *m*/*z* 174 (49, M^+), 457 (80), 274 (100). Anal. Calcd for $C_{25}H_{34}N_2O_7$ (474.55): C, 63.28; H, 7.22. Found: C, 63.21, H, 7.13.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-5-methoxybenzoate (6). The *tert*-butyllithium-promoted metalation of *tert*-butyl (4-methoxyphenyl)carbamate, the trapping with carbon dioxides and the workup were carried out as described for the preparation of the isomer **2** (see section 1). After treatment with diazomethane a pale yellow solid was isolated. According to gas chromatography (30 m, DB-1701, 220 °C), the crude product was composed of the regioisomers **5** and **6** in the ratio of 12:88, 86% yield. Pure ester **6** was obtained after recrystallization (from dichloromethane/hexane 1:3) in form of white needles: mp 54−56 °C; yield 55%; ^{1}H-NMR δ 9.98 (1 H, s, broad), 8.35 (1 H, d, J = 9.3), 7.48 (1 H, d, J = 3.1), 7.10 (1 H, dd, J = 9.3, 3.1), 3.92 (3 H, s), 3.80 (3 H, s), 1.52 (9 H, s); MS *m*/*z* 281 (24, M^+), 225 (38, 181 (100). Anal. Calcd for $C_{14}H_{19}NO_5$ (281.31): C, 59.78; H, 6.81. Found: C, 59.71; H, 6.99.

Di-(*tert*-butyl 2,3′-Hydroxymethylenebis[(4-methoxyphenyl)carbamate] (8) and Di(*tert*-butyl 2,2′-Hydroxymethylenebis[(4-methoxyphenyl)carbamate] (9). The carbon dioxide was replaced by methyl formate in a reaction analogously conducted as the one described in the preceding paragraph. The crude product contained **8** and **9** as the minor and main component, respectively. The separation was achieved by chromatography using silica gel (500 mL) as the support and a 1:4 (v/v) mixture of ethyl acetate and hexane as the eluent. Biscarbamate **8**: white platelets; mp 66−70 °C dec; yield 10%; ^{1}H-NMR δ 7.6 (3 H, m), 6.88 (1 H, s, broad), 6.87 (1 H, d, J = 8.9), 6.83 (1 H, dd, J = 8.9, 3.0), 6.73 (1 H, d, J = 2.8), 6.35 (1 H, s, broad), 6.06 (1 H, d, J = 3.6), 3.85 (3 H, s), 3.74 (3 H, s), 3.44 (1 H, s, broad), 1.48 (9 H, s), 1.46 (9 H, s); MS *m*/*z* 474 (36, M^+), 374 (42), 317 (44), 269 (100). Anal. Calcd for $C_{25}H_{34}N_2O_7$ (474.55): C, 63.28; H, 7.22. Found: C, 63.12; H, 7.29. Biscarbamate **9**: white platelets; mp 143−145 °C dec; yield 50%; ^{1}H-NMR δ 7.52 (2 H, s, broad), 7.05 (2 H, s, broad), 6.81 (2 H, dd, J = 8.8, 3.0), 6.69 (2 H, s, broad), 5.85 (1 H, d, J = 2.9), 4.10 (1 H, d, broad), 3.70 (6 H, s), 1.45 (18 H, s); MS 474 (19, M^+), 279 (31), 240 (100). Anal. Calcd for $C_{25}H_{34}N_2O_7$ (474.55): C, 63.28; H, 7.22. Found: C, 63.16; H, 7.24.

(3) Reactions Involving *N*-Carbamoyl-Protected *p*-Anisidine. *N*′-(4-Methoxyphenyl)-*N*,*N*-dimethylurea. A solution of *p*-anisidine (25 g, 0.20 mol), *N*,*N*-dimethylcarbamoyl chloride (18 mL, 21 g, 0.20 mol), and pyridine (16 mL, 16 g, 0.20 mol) in dichloromethane (0.15 L) was heated to reflux for 20 h, before being washed with 1 M hydrochloric acid (2 × 0.10 L) and water (2 × 0.10 L), dried, and evaporated. The colorless residue was crystallized from a 1:1 (v/v) mixture of dichloromethane and hexane: mp 128.5−130.5 °C (from dichloromethane/hexane 1:3); white needles; yield 80%; ^{1}H-NMR δ 7.25 (2 H, d, J = 9.0), 6.81 (2 H, d, J = 9.0), 6.38 (1 H, s, broad), 3.76 (3 H, s), 2.97 (6 H, s); MS *m*/*z* 194 (23, M^+), 149 (32), 72 (100). Anal. Calcd for $C_{10}H_{14}N_2O_2$ (194.23): C, 61.84; H 7.27. Found: C, 61.84; H, 7.15.

***N*,*N*-Diethyl-*N*′-(4-methoxyphenyl)urea** was obtained analogously by employing *N*,*N*-diethylcarbamoyl chloride (25 mL, 27 g, 0.20 mol): mp 60.5−62.0 °C (from dichloromethane/hexane 1:3); white needles; yield 55%; ^{1}H-NMR δ 7.28 (2 H, d, J = 8.9), 6.83 (2 H, d, J = 9.0), 6.18 (1 H, s, broad), 3.78 (3 H, s), 3.36 (4 H, q, J = 7.1), 1.21 (6 H, t, J = 7.1); MS *m*/*z* 223 (23, $M^+ + 1$); 149 (2); 100 (100). Anal. Calcd for $C_{12}H_{18}N_2O_2$ (222.29): C 64.84; H, 8.16. Found: C, 64.81; H, 8.08.

Methyl 2-[[(Dimethylamino)carbonyl]amino]-5-methoxybenzoate [2-(*N*′,*N*′-Dimethylureido)-5-methoxybenzoic Acid Methyl Ester (10)], *N*-[[(2-Carboxy-4-methoxyphenyl)amino]carbonyl]-*N*-(methylamino)acetic Acid (11), and 3-(4-Methoxyphenyl)-1-methylimidazolidine-2,4-dione (12). At −75 °C, *tert*-butyllithium (50 mmol) in pentane (33 mL) was added to a solution of *N*′-(4-methoxyphenyl)-*N*,*N*-

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dimethylurea (4.9 g, 25 mmol) in tetrahydrofuran (67 mL). After 2 h of stirring at −25 °C, the mixture was poured on an excess of freshly crushed dry ice. The solvents were evaporated, and water (0.10 L) was added to the residue. Starting material (36%) was recovered when the aqueous phase was extracted with diethyl ether (2 × 50 mL). Upon acidification to pH 5, a white precipitate was formed, which was collected and treated with an ethereal solution of diazomethane until the yellow color persisted. After evaporation of the ether, the ester **10** was isolated as pale yellow platelets: mp 158−160 °C (after recrystallization from dichloromethane/hexane 1:3); yield 36%; ^{1}H-NMR δ 10.35 (1 H, s, broad), 8.51 (1 H, d, J = 9.2), 7.48 (1 H, d, J = 3.0), 7.11 (1 H, dd, J = 9.2, 3.0), 3.91 (3 H, s), 3.80 (3 H, s), 3.08 (6 H, s); MS m/z 252 (71, M^+), 207 (31), 176 (29); 72 (100). Anal. Calcd for $C_{12}H_{16}N_2O_4$ (252.27): C, 57.13; H, 6.39. Found: C, 57.23; H, 6.41. The aqueous filtrate was extracted with diethyl ether (3 × 50 mL) and dichloromethane (2 × 50 mL). After evaporation of the solvent, the residue was triturated with dichloromethane (25 mL). The insoluble white solid was collected and recrystallized from acetone to give the diacid **11**: white prims; mp 140−144 °C dec (from acetone); yield 7%; ^{1}H-NMR δ 8.29 (1 H, d, J = 9.2), 7.56 (1 H, d, J = 3.1), 7.12 (1 H, dd, J = 9.2, 3.1), 4.14 (2 H, s), 3.79 (3 H, s), 3.14 (3 H, s); MS m/z 283 (3, $M^+ + 1$), 264 (100), 247 (41), 220 (14). Anal. Calcd for $C_{12}H_{14}N_2O_6$ (282.25): C, 51.06; H, 5.00. Found: C, 50.89; H, 5.20. Column chromatography (elution from 500 mL of silica gel with ethyl acetate/hexane 1:4) of the contents of the mother liquors afforded the imidazolidinedione **12**: white platelets; mp 113.5−115.0 °C (from diethyl ether) lit.[18] mp 117−120 °C; yield 11%; ^{1}H-NMR δ 7.29 (2 H, d, J = 9.0), 6.97 (2 H, d, J = 9.0), 4.03 (2 H, s), 3.82 (3 H, s), 3.08 (3 H, s); MS m/z 220 (96, M^+), 149 (100); 134 (34). Anal. Calcd for $C_{11}H_{12}N_2O_3$ (220.23): C, 59.99; H, 5.49. Found: C, 60.20; H, 5.26.

When the amount of *tert*-butyllithium was increased to 2.5 equiv, carboxylation after 6 h gave the products **10**, **11**, and **12** in 31%, 11%, and 23% yield, and after metalation during 2 h with 5.0 equiv in 10%, 35% and 5% yield. Still 18−20% of unconsumed starting material were recovered. When the metalation was accomplished with 2 equiv of each *tert*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine during 2 h in diethyl ether at −50 °C, 15% of **10**, 30% of **12**, and 50% of starting material were isolated.

Methyl 2-[[(diethylamino)carbonyl]amino]-5-methoxybenzoate and methyl 5-[[(diethylamino)carbonyl]amino]-2-methoxybenzoate were obtained in 45% and, respectively, 15% yield, when the sequence consisting of metalation with *tert*-butyllithium in tetrahydrofuran, carboxylation, and treatment with diazomethane was performed as described above in detail for the *N*′,*N*′-dimethyl analogue, and in yields of 22% and, respectively, 55%, when tetrahydrofuran was replaced by diethyl ether. **2-Amido-5-methoxy isomer**: mp 87.5−89.5 °C (from dichloromethane/hexane 1:3); colorless platelets; ^{1}H-NMR δ 10.31 (1 H, s, broad), 8.52 (1 H, d, J = 9.3), 7.47 (1 H, d, J = 3.0), 7.10 (1 H, dd, J = 9.3, 3.1), 3.91 (3 H, s), 3.80 (3 H, s), 3.43 (4 H, q, J = 7.1), 1.25 (6 H, t, J = 7.1); MS m/z 281 (100, $M^+ + 1$), 249 (12); 100 (4). Anal. Calcd for $C_{14}H_{20}N_2O_4$ (280.32): C, 59.99; H, 7.19. Found: C, 59.94; H, 7.28. **5-Amido-2-methoxy isomer**: mp 84.0−85.5 °C (from dichloromethane/hexane 1:3); colorless prisms; ^{1}H-NMR δ 7.71 (1 H, d, J = 2.8), 7.64 (1 H, dd, J = 8.9, 2.8), 6.89 (1 H, d, J = 8.9), 6.47 (1 H, s, broad), 3.86 (6 H, s), 3.36 (4 H, q, J = 7.1), 1.20 (6 H, t, J = 7.1); MS m/z 281 (100, $M^+ + 1$); 249 (3); 100 (9). Anal. Calcd for $C_{14}H_{20}N_2O_4$ (280.33): C 59.99; H, 7.19. Found: C, 59.79; C, 7.18.

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