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Meta Functionalization of Anilines and Phenol

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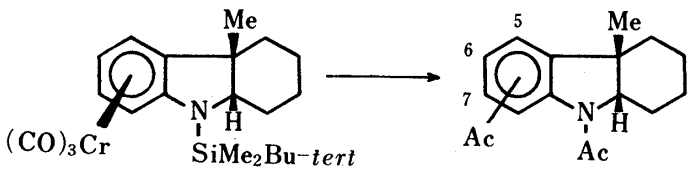
Base-promoted proton abstraction from π-(*N*-*tert*-butyldimethylsilyl-*N*-methylaniline)chromium tricarbonyl (**3**) took place predominantly at the *meta* position and variously *meta*-substituted *N*-methylacetanilides **4** were obtained after reactions with electrophiles followed by oxidative decomplexation and *N*-acetylation. Application of the present method to variously *N,N*-disubstituted anilines **5** and phenols **7** was then examined and the corresponding *meta* substituted anilines **6** and phenol **9** were obtained.

Keywords——metalation of aromatic ring; chromium tricarbonyl complex; *tert*-butyl dimethylsilyl protecting group; *meta*-substituted anilines; *meta*-substituted phenol; electrophilic substitution

Base-promoted proton abstraction from an aromatic ring is known to be facilitated by the presence of a functionalized substituent on the aromatic ring and the metalation takes place at the *ortho* position to the functional group.[1] Recently, it became apparent that even benzene itself was metalated when the aromatic ring was activated by chromium tricarbonyl complex formation,[2] and π-(alkylbenzenes)chromium tricarbonyl or π-(*N,N*-dimethylaniline)chromium tricarbonyl produced, after proton abstraction with butyllithium followed by alkyl halide treatment, the three possible *ortho, meta,* and *para* alkyl compounds, the *meta* isomers being slightly predominant.[2b] In view of the fact that introduction of substituents at the *meta* position to an electron-donating group is difficult, it was considered to be worthwhile to investigate the above reaction further.

We anticipated that, even in aniline or phenol derivatives, if the *ortho* position was masked by a bulky *N*- or *O*-substituent(s) and the aromatic protons were activated by chromium tricarbonyl complex formation, metalation should take place on the *meta* or *para* position. In fact, as part of our efforts to introduce functionalized substituents on the aromatic rings of indoline alkaloids, π-(9-*tert*-butyldimethylsilyl-4*a*-methyl-1,2,3,4,4*a*,9*a*-hexahydrocarbazole)chromium tricarbonyl (**1**) was subjected to a series of reactions (lithiation by *n*-BuLi–*N,N,N′,N′*-tetramethylethylenediamine (TMEDA) followed by the addition of acetaldehyde, oxidative decomplexation by iodine, *N*-acetylation, and Jones oxidation of the resulting alcohol), and the 5-, 6-, and 7-acetyl derivatives **2a**, **b**, **c** were obtained in a ratio of 2:1:7 (total yield, 59%).[3] This unexpectively high *meta*/*para* substitution ratio (9/1) and the fact that the 8-acetyl isomer could not be detected prompted us to investigate this reaction in more detail in a simplified system.[4]



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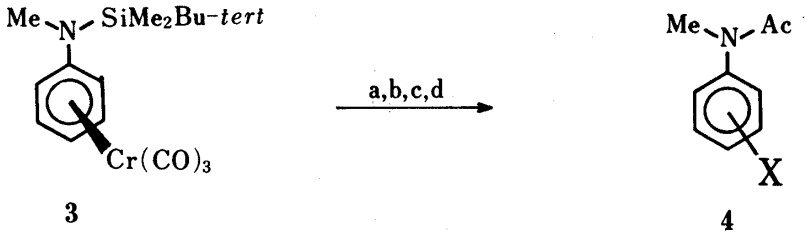
2a : 5-Ac
2b : 6-Ac
2c : 7-Ac

Chart 1

Initially, π-(*N*-*tert*-butyldimethylsilyl-*N*-methylaniline)chromium tricarbonyl (**3**), prepared in high yield from π-(aniline)chromium tricarbonyl by *N*-silylation followed by *N*-methylation, was chosen as a substrate. Metalation of **3** was carried out in two ways: i) *n*-BuLi (2 eq)–TMEDA (3 eq) in tetrahydrofuran (THF) at −60 °C for 3 h ——method A or ii) *n*-BuLi (4 eq) in THF at −40 °C for 30 min ——method B.[2b] The lithiated chromium tricarbonyl complex was quenched with various electrophiles and subjected to oxidative decomplexation by treatment with excess iodine in 10% HCl[5]/THF in the presence of camphorsulfonic acid (CSA, 1.5 eq). The resulting variously substituted *N*-methylanilines were then *N*-acetylated to afford the *N*-methylacetanilide derivatives **4a**—**f**. The results are shown in Table I.

As was expected, no *ortho*-substituted products were obtained. It is noteworthy that when carbonyl electrophiles (aldehydes or dimethylformamide) were used, a remarkably high *meta* to *para* substitution ratio was obtained (entries 1—4). Even in entries 5—7, predominance of *meta* substitution (*m*:*p*=85:15) is evident, compared to the results obtained by metalation and subsequent alkyl halide treatment of π-(ethylbenzene)-, π-(*tert*-butylbenzene)-, or π-(*N*,*N*-dimethylaniline)chromium tricarbonyl, where the substitution ratios on *meta* and *para* positions were roughly estimated to be 2:1, 3:2, or 3:1, respectively.[2b,6] Thus, the *tert*-butyldimethylsilyl protecting group was found to be quite effective not only for blocking the *ortho* position but also for directing *meta* selectivity, although the reason why carbonyl electrophiles gave a much better *meta*/*para* ratio than other electrophiles remained unclear.

Then, we investigated the influence of *N*-substituents on the substitution pattern of the products in the same reactions as mentioned above. The compounds **5b**, **c** were prepared in



3 **4**

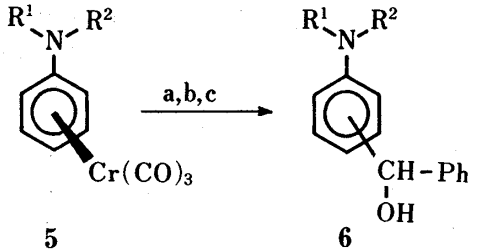
(a) *n*-Buli(TMDEA)/THF, (b) electrophiles, (c) I_2/CSA/THF–10% HCl, (d) Ac_2O/Py.

Chart 2

TABLE I. Lithiation of π-(*N*-*tert*-Butyldimethylsilyl-*N*-methylaniline) chromium Tricarbonyl (**3**) and Reactions with Electrophiles

Entry	Electrophile	Method of metalation[a]	Product	X	Yield (%)	Ratio of isomers[c] *ortho*:*meta*:*para*
1	PhCHO	A	**4a**[b]	CH(OH)Ph	69	0 : 98 : 2
2	PhCHO	B	**4a**[b]	CH(OH)Ph	62	0 : 95 : 5
3	MeCHO	A	**4b**[b]	CH(OH)Me	57	0 : 96 : 4
4	$HCONMe_2$	A	**4c**	CHO	61	0 : 98 : 2
5	MeI	B	**4d**	Me	73	0 : 86 : 14
6	MeSSMe	A	**4e**	SMe	73	0 : 85 : 15
7	PhCN	A	**4f**	COPh	73	0 : 86 : 14

a) Method A: *n*-BuLi (2 eq)-TMEDA (3 eq)/−60°C/3 h; Method B: *n*-BuLi (4 eq)/−40°C/30 min.
b) In these cases, *N*, *O*-diacetylation takes place on acetylation with Ac_2O–Py. Subsequent KOH/MeOH treatment causes selective de-*O*-acetylation affording **4a**, **b**.
c) The isomer ratios were determined by gas chromatography. The structures of the products were unequivocally confirmed by comparing the IR, NMR, and GC spectra with those of authentic samples, except for **4e**.



5 6

a: $R^1=R^2=Me$
b: $R^1=Me$, $R^2=CH_2Bu\text{-}tert$
c: $R^1=Et$, $R^2=CH_2Bu\text{-}tert$
d: $R^1=Me$, $R^2=Ph$
e: $R^1=Et$, $R^2=Ph$
f: $R^1=R^2=Ph$

(a) *n*-BuLi/TMEDA/THF/(see Table I, footnote *a*),method A), (b) phCHO, (c) I_2/CSA/THF–10%HCl.

Chart 3

TABLE II. Reaction of Lithio π-(Anilines) chromium Tricarbonyl with Benzaldehyde

Entry	Substrate	R^1	R^2	Product	Yield (%)	Ratio of isomers[a] *ortho:meta:para*
1	**5a**	Me	Me	**6a**	86	31 : 50 : 19
2	**5b**	Me	$CH_2Bu\text{-}tert$	**6b**	74	14 : 76 : 10
3	**5c**	Et	$CH_2Bu\text{-}tert$	**6c**	64	1 : 99 : 0
4	**5d**	Me	Ph	**6d**	64	29 : 71 : 0
5	**5e**	Et	Ph	**6e**	68	17 : 83 : 0
6	**5f**	Ph	Ph	**6f**	75	0 : 100 : 0

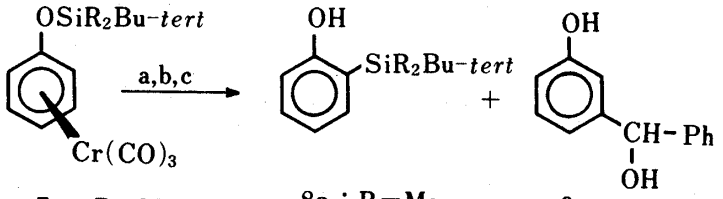
a) The isomer ratios were determined by gas chromatography. The structures of the products were unequivocally confirmed by analysis of the IR, NMR, and GC-mass spectra.

the same way as described for **3**. The compounds **5d—f** were prepared by the forced nucleophilic substitution reactions[5] of π-(chlorobenzene)chromium tricarbonyl[7] with potassium salts of *N*-methylaniline, *N*-ethylaniline, or diphenylamine in the presence of 18-crown-6. These *N,N*-disubstituted chromium tricarbonyl complexes were subjected to a series of reactions using benzaldehyde as an electrophile (method A). The results are shown in Table II. The data for π-(*N,N*-dimethylaniline)chromium tricarbonyl (**5a**)[7] are also presented for comparison.

In the case of the *N*-methyl-*N*-neopentyl derivative **5b**, selectivity was much reduced compared to that of **3** and appreciable amounts of both *ortho* and *para* isomers were obtained (entry 2) although the results were much better than entry 1. However, when the *N*-ethyl-*N*-neopentyl derivative **5c** was used, the *meta* isomer was obtained almost as a sole product (entry 3). *N*-Phenyl derivatives **5d, e** gave substantial amounts of the *ortho* isomers, but again none of the *para* isomers was obtained (entries 4, 5). The *N,N*-diphenyl derivative **5f** gave only a *meta* isomer in good yield. It should be recalled that metalation of triphenylamine with *n*-BuLi in the presence of copper bronze took place at the *meta* position, but the yield was only 7%.[8]

Then, we examined whether the present method is applicable to phenol systems. When π-(*tert*-butyldimethylsilyloxybenzene)chromium tricarbonyl (**7a**) was subjected to the series of reactions, 2-*tert*-butyldimethylsilylphenol (**8a**) and 3-α-hydroxybenzylphenol (**9**) were obtained in 35 and 40% yields, respectively. Formation of **8a** clearly indicates that *ortho* lithiation took place in this case, but here again, no *para* isomer could be obtained. Furthermore, when the phenol oxygen was blocked with a *tert*-butyldiphenylsilyl group, formation of **8b** was suppressed to 19% but that of **9** improved to 48%. Thus, electrophilic substitution was proved to take place even in phenol when the reactivity was properly modulated by simple derivatization.

Trahanovsky[2b] has suggested the possibility that proton abstraction is preceded by



7a : R=Me
7b : R=Ph

8a : R=Me
8b : R=Ph

9

(a) *n*-BuLi/TMEDA/THF,(b) PhCHO, (c) I_2/CSA/THF-10%HCl.

Chart 4

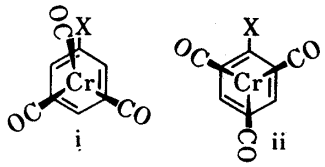


Chart 5

formation of an adduct of butyllithium to an oxygen of a carbonyl ligand and then a butyl anion abstracts a hydrogen from the aromatic carbon eclipsed to the carbonyl ligand.[9] In fact, π-(*N-tert*-butyldimethylsilyl-*N*-methylaniline)chromium tricarbonyl (**3**) was determined to have an eclipsed structure i [X=N(Me)$SiMe_2$Bu-*tert*] by X-ray crystallography[10,11] although a large substituent exists on the nitrogen atom. This eclipsed structure i is expected to be maintained even in solution, because it has been claimed that when X is an electron-donating group, an eclipsed conformer i is favored over other conformers, including an eclipsed conformer ii, both in the solid phase[12] and in solution,[13] although the tricarbonyl group in **3** is generally considered to be rotating rapidly in solution. The high *meta* substitution ratio obtained in this system could be rationalized, at least in part,[14] in terms of the above assumption.

Experimental

All melting points were taken in open capillaries with a Mitamura Riken melting point apparatus (type 1-128, No 146) and are uncorrected. Infrared (IR) spectra were measured on Hitachi 215 and JASCO A-102 spectrophotometers, nuclear magnetic resonance (NMR) spectra on JEOL C-60HL, JEOL FX-60, Varian HA-100D, and JEOL FX-400 instruments using tetramethylsilane as an internal standard, and GC-MS spectra on a Hitachi RMU-6MG mass spectrometer. Gas chromatography (GC) was carried out on a Shimadzu GC-4CM gas chromatograph using a glass column (2 m×3 mm) packed with 1.5% OV-17 on Shimalite W (80—100 mesh).

π-(*N-tert*-Butyldimethylsilylaniline)chromium Tricarbonyl——Under an atmosphere of argon, *n*-BuLi (10% w/v hexane solution, 26.8 ml) was added dropwise below −60°C to a THF (30 ml) solution of π-(aniline)chromium tricarbonyl (8.0 g) prepared according to Nicholls' method.[7] The reaction mixture was then warmed to room temperature and cooled to 0°C again. A THF (8 ml) solution of *tert*-BuMe_2SiCl (6.317 g, 1.2 eq) was added dropwise at 0°C and the whole was stirred for 1 h at room temperature, then 20% NH_4Cl was added and the mixture was extracted with ether. The ether extract was washed with sat. brine, dried over Na_2SO_4, and concentrated to give 11.75 g of a yellow solid (98% yield). Recrystallization of this product from ether–hexane gave yellow prisms of mp 160—161°C. IR ν_{max}^{Nujol} cm^{-1}: 3360 (NH), 1950, 1860, 1840 (C≡O), 1535 (Ar–N). *Anal.* Calcd for $C_{15}H_{21}CrNO_3Si$: C, 52.46; H, 6.16; N, 4.08. Found: C, 52.46; H, 6.16; N, 4.02.

π-(*N-tert*-Butyldimethylsilyl-*N*-methylaniline)chromium Tricarbonyl (3)——*n*-BuLi in hexane (13.1 ml, 1.2 eq) was added dropwise below −60°C to a THF (40 ml) solution of the *N*-silylated compound mentioned above (5.84 g) under an argon atmosphere. The reaction mixture was stirred for 1 h at this temperature. A THF (2 ml) solution of MeI (1.59 ml, 1.5 eq) was then added dropwise and the whole was warmed to room temperature with stirring. After 1 h, 20% NH_4Cl was added and the mixture was extracted with ether. The ether extract was washed with sat. brine, dried over Na_2SO_4, and concentrated to give a yellow solid, which was dissolved in CH_2Cl_2–ether again and filtered through a celite pad. The solvents were removed to give 6.07 g of a yellow solid (quant.), which was recrystallized from ether–hexane to afford yellow prisms of mp 108—109°C. IR ν_{max}^{Nujol} cm^{-1}: 1970, 1940, 1870, 1845 (C≡O), 1530 (Ar–N). NMR (d_6-acetone) δ: 0.36 (6H, s, $SiCH_3$), 1.04 (9H, s, *tert*-Bu), 2.91 (3H, s, NCH_3), 5.05 (1H, t, J=6.4 Hz, *para*-H), 5.28 (2H, d, J=6.6 Hz, *ortho*-H), 5.81 (2H, dd, J=6.4 and 7.3 Hz, *meta*-H). MS *m/e*: 357 (M^+), 301 (M^+−2CO), 273 (M^+−3CO, 100%). *Anal.* Calcd for $C_{16}H_{23}CrNO_3Si$: C, 53.76; H, 6.48; N, 3.92. Found: C, 53.82; H, 6.47; N, 3.87.

3-α-Hydroxybenzyl-*N*-methylacetanilide (4a)——Method A: A mixture of *n*-BuLi/hexane (5.91 ml, 2.2 eq) and TMEDA (1.61 g, 3.3 eq) was added dropwise to a THF (15 ml) solution of **3** (1.5 g, 4.2 mmol) below −60°C under an argon atmosphere. The mixture was stirred for 3 h at −60°C, then 3 ml of PhCHO (7 eq)

was added dropwise and the whole was stirred for 30 min at −60 °C then for 1 h at room temperature. Next, 20% NH_4Cl was added and the mixture was extracted with ether. The extract was washed with 40% $NaHSO_3$ and sat. brine successively, dried over Na_2SO_4, and concentrated. The residue was dissolved in 14 ml of THF. The solution was cooled to 0 °C, 8 ml of 10% HCl and 1.46 g of CSA (1.5 eq) were added, and then 4.2 g of iodine was added portionwise. The whole was stirred for 30 min at room temperature. After the addition of 40% $NaHSO_3$, the mixture was washed with ether, made alkaline by the addition of 20% NaOH, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated to give a red oil, which was immediately acetylated with Ac_2O (2 ml) and pyridine (3 ml). After being stirred overnight, the mixture was diluted with ether and washed with 10% HCl, 10% NaOH, and sat. brine successively. The ether layer was dried over Na_2SO_4 and concentrated. The resulting residue was dissolved in 10% KOH/MeOH (12 ml) and stirred for 30 min at room temperature. Water was added to this solution and the mixture was extracted with ether. The extract was washed with sat. brine, dried over Na_2SO_4, and concentrated to give a yellow oil, which was chromatographed on silica gel. Elution with EtOAc–benzene (2:1) gave 742 mg of **4a** as a colorless oil (69% yield), which was analyzed by gas chromatography. The ratio of isomers is presented in Table I and physical properties are listed in Table III.

Method B: *n*-BuLi/hexane (7.16 ml, 4 eq) was added dropwise to a THF (10 ml) solution of **3** (1.0 g, 2.8 mmol) at −40 °C under an argon atmosphere. The mixture was stirred for 30 min at −40 °C, then 2 ml of PhCHO was added dropwise and the whole was stirred for 30 min at −40 °C and then for 1 h at room temperature. The reaction mixture was worked up in the same manner as in method A.

3-1′-Hydroxyethyl-*N*-methylacetanilide (4b)——**4b** was obtained in the same manner as described for the preparation of **4a** (method A) using acetaldehyde in this case. The yield and the ratio of isomers are shown in Table I and physical properties are listed in Table III.

3-Formyl-*N*-methylacetanilide (4c)——DMF (5 ml) was added to a cooled (−60 °C) solution of lithiated **3**, which was prepared in the same manner as described for **4a** (method A). The reaction mixture was stirred for 30 min at −60 °C and for 1 h at room temperature, then poured into conc. HCl containing crushed ice. The mixture was extracted with ether and the ether layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was subjected to the decomplexation with iodine followed by acetylation in the same manner as described for **4a**. The crude product thus obtained was chromatographed on silica gel. Elution with EtOAc–benzene (1:1) gave a white solid, which was recrystallized from CCl_4 to afford white needles of mp 108—109 °C. The yield and the ratio of isomers are shown in Table I and physical properties are listed in Table III.

3-Methyl-*N*-methylacetanilide (4d-*meta*) and 4-Methyl-*N*-methylacetanilide (4d-*para*)——**4d** was obtained in the same manner as described for **4a** (method A or B) using MeI (5 eq) as an electrophile in this case. The product was recrystallized from hexane to give colorless prisms of mp 73—74.5 °C (*meta* isomer). The yield and the ratio of isomers are shown in Table I and physical properties are listed in Table III.

3-Methylthio-*N*-methylacetanilide (4e-*meta*) and 4-Methylthio-*N*-methylacetanilide (4e-*para*)——**4e** was obtained in the same manner as described for **4a** (method A) using dimethyldisulfide (3 eq) as an electrophile in this case. After analysis by gas chromatography, the isomeric mixture was subjected to medium pressure liquid chromatography on a Lobar column. Elution with EtOAc–hexane (3:2) gave the *meta* and *para* isomers in highly pure form, respectively. The yield and the ratio of isomers are shown in Table I and physical properties are listed in Table III.

3-Benzoyl-*N*-methylacetanilide (4f-*mata*) and 4-Benzoyl-*N*-methylacetanilide (4f-*para*)——The crude chromium tricarbonyl complex, which was obtained by the reaction of lithiated **3** with PhCN (5 eq), in the same manner as described for **4a**, was treated with iodine in a usual way. After the addition of 40% $NaHSO_3$, the whole was heated under reflux for 1 h for hydrolysis of the imine. The mixture was washed with ether, made alkaline by the addition of 20% NaOH, and then extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated to give benzoyl-*N*-methylaniline, which was acetylated in a usual manner. The crude product was chromatographed on silica gel using EtOAc–benzene (2:1) as an eluent to give a yellowish solid, which was recrystallized from ether–pentane to afford white crystals of mp 60—61 °C (*meta* isomer). The yield and the ratio of isomers are shown in Table I and physical properties are listed in Table III.

π-(*N*-Mehyl-*N*-neopentylaniline)chromium Tricarbonyl (5b)——*N*-Neopentylaniline (3.7 g) [prepared from *N*-pivaloylaniline by $LiAlH_4$ reduction] was dissolved in diglyme (50 ml)-cyclohexane (65 ml) and after the addition of $Cr(CO)_6$ (9.98 g, 2 eq), the whole was refluxed for 95 h (bath temp.; 125—130 °C) under an argon atmosphere. $Cr(CO)_6$ that sublimed inside the reflux condenser was occasionally returned mechanically to the reaction flask. The reaction solution was then concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2–ether. The resulting orange solution was filtered through a celite pad and concentrated again to give a crystalline mass, which was washed with hexane to afford 6.18 g (91% yield) of a yellow powder [mp 148—150 °C (dec.)]. π-(*N*-Neopentylaniline)chromium tricarbonyl (1.0 g) in THF (5 ml) was added dropwise to a suspension of KH (356 mg, 1.2 eq) in THF (6 ml) containing 220 mg of 18-crown-6 (0.25 eq) under an argon atmosphere. The mixture was stirred for 30 min at room temperature and then cooled to 0 °C. MeI (0.27 ml, 1.3 eq) in THF (1 ml) was added dropwise to this solution and the whole was stirred for 1 h at room temperature. Next, 20% NH_4Cl was added and the mixture was extracted with ether. The ether extract was

TABLE III. *meta*- or *para*-Substituted-*N*-methylacetanilides (**4**)

Compd.	mp (°C)	IR ν_{max}^{neat} cm^{-1} *a)*	NMR ($CDCl_3$) δ
4a-*meta*[b]	Oil	3550 (br), 1635, 1600	1.79 (3H, s, $NCOCH_3$), 3.14 (1H, br s, OH), 3.20 (3H, s, NCH_3) 5.81 (1H, s, C<u>H</u>-OH), 6.86—7.45 (9H, m, Ar-H).
4b-*meta*[c]	Oil	3350 (br), 1640, 1600, 1585	1.51 (3H, d, J=6.6 Hz, CH-C<u>H</u>$_3$), 1.88 (3H, s, $NCOCH_3$), 2.67 (1H, s, OH), 3.25 (3H, s, NCH_3), 4.91 (1H, q, J=6.6 Hz, C<u>H</u>-CH_3), 6.92—7.45 (4H, m, Ar-H).
4c-*meta*[d]	108—110	1690, 1685, 1600, 1585	1.97 (3H, s, $NCOCH_3$), 3.29 (3H, s, NCH_3), 7.42—8.02 (4H, m, Ar-H) 10.07 (1H, s, C<u>H</u>O).
4d-*meta*[e]	73—74.5	1655, 1605, 1585	[i]1.77 (3H, s, $NCOCH_3$), 2.37 (3H, s, Ar-CH_3), 3.06 (3H, s, NCH_3), 6.80—7.38 (4H, m, Ar-H).
4d-*para*[f]	76.5—78	1670, 1610	[i]1.75 (3H, s, $NCOCH_3$), 2.37 (3H, s, Ar-CH_3), 3.15 (3H, s, NCH_3), 6.89—7.14 (4H, m, Ar-H).
4e-*meta*	Oil	1660, 1580	[i]1.80 (3H, s, $NCOCH_3$), 2.47 (3H, s, SCH_3), 3.15 (3H, s, NCH_3), 6.73—7.36 (4H, m, Ar-H).
4e-*para*	Oil	1660, 1590	[i]1.76 (3H, s, $NCOCH_3$), 2.45 (3H, s, SCH_3), 3.12 (3H, s, NCH_3), 6.86—7.10 (4H, m, Ar-H).
4f-*meta*[g]	60—61	1655, 1590, 1580	1.98 (3H, s, $NCOCH_3$), 3.09 (3H, s, NCH_3), 7.36—8.01 (9H, m Ar-H).
4f-*para*[h]	100.5—102	1655, 1590, 1570	2.03 (3H, s, $NCOCH_3$), 3.36 (3H, s, NCH_3), 7.25—8.05 (9H, m Ar-H).

a) Nujol mulls were used for crystalline compounds.
b) Indentical with an authentic sample derived from 3-aminobenzyl alcohol.
c) Indentical with an authentic sample derived from 3-aminoacetophenone.
d) Indentical with an authentic sample derived from 3-aminobenzyl alcohol.
e) Indentical with an authentic sample derived from *N*-methyl-*m*-toluidine.
f) Date for an authentic sample derived from *N*-methyl-*p*-toluidine are presented.
g) Indentical with an authentic sample derived from 3-aminobenzyl alcohol.
h) Date for an authentic sample derived from 4-aminobenzophenone are presented.
i) In CCl_4.

washed with sat. brine, dried over Na_2SO_4, and concentrated to give a yellow residue, which was treated with hexane, and the resulting yellow powder was filtered off (985 mg, 94% yield). Recrystallization from ether–hexane gave yellow prisms of mp 112—113 °C. IR ν_{max}^{Nujol} cm^{-1}: 1940, 1870, 1840 (C≡O), 1540 (Ar–N). NMR (d_6-acetone) δ: 1.00 (9H, s, *tert*-Bu), 2.98 (3H, s, N-CH_3), 3.09 (2H, s, C<u>H</u>$_2$-Bu-*tert*), 5.01 (1H, t, J=6.0 Hz, *para*-H), 5.16 (2H, d, J=7.0 Hz, *ortho*-H), 5.83 (2H, dd, J=6.0 and 7.0 Hz, *meta*-H). *Anal.* Calcd for $C_{15}H_{19}CrNO_3$: C, 57.51; H, 6.11; N, 4.47. Found: C, 57.34; H, 6.11; N, 4.42.

π-(*N*-Ethyl-*N*-neopentylaniline)chromium Tricarbonyl (5c)——In the same manner as described above, but using EtI in this case, **5c** was obtained as a yellow powder in 97% yield. Recrystallization from ether–hexane gave yellow prisms of mp 104—105 °C. IR ν_{max}^{Nujol} cm^{-1}: 1940, 1850 (C≡O), 1540 (Ar–N). NMR (d_6-acetone) δ: 1.03 (9H, s, *tert*-Bu), 1.26 (3H, t, J=7.1 Hz, CH_2C<u>H</u>$_3$), 3.13 (2H, s, C<u>H</u>$_2$-Bu-*tert*), 3.41 (2H, q, J=7.1 Hz, C<u>H</u>$_2CH_3$), 4.98 (1H, t, J=6.1 Hz, *para*-H), 5.17 (2H, d, J=7.1 Hz, *ortho*-H), 5.80 (2H, dd, J=6.1 and 7.6 Hz, *meta*-H). *Anal.* Calcd for $C_{16}H_{21}CrNO_3$: C, 58.87; H, 6.46; N, 4.28. Found: C, 58.56; H, 6.48; N, 4.22.

π-(*N*-Methyl-*N*-phenylaniline)chromium Tricarbonyl (5d)——*N*-Methylaniline (633 mg, 1.5 eq) in THF (2 ml) was added dropwise to a suspension of KH (536 mg, 1.5 eq) in THF (12 ml) containing 265 mg of 18-crown-6 (0.25 eq) at room temperature under an argon atmosphere. The mixture was stirred for 1 h at room temperature and then cooled to 0 °C. π-(Chlorobenzene)chromium tricarbonyl[7] (1.0 g) was added all at once to the reaction mixture and the whole was stirred for 30 min at 0 °C. The solution was allowed to warm to room temperature, then 20% NH_4Cl was added and the resulting mixture was extracted with ether. The extract was washed with cold 10% HCl and water successively, dried over Na_2SO_4, and concentrated to give a yellow crystalline solid, which was washed with hexane to afford 1.22 g of a yellow powder (96% yield). Recrystallizatin from CH_2Cl_2–hexane gave yellow prisms of mp 130—131 °C. IR ν_{max}^{Nujol} cm^{-1}: 1945, 1835 (C≡O), 1590 (Ar), 1535 (Ar–N). NMR (d_6-acetone) δ: 3.30 (3H, s, N-CH_3), 5.02 (2H, d, J=7.3 Hz, *ortho*-H), 5.04 (1H, t, J=5.9 Hz, *para*-H), 5.81 (2H, dd, J=5.9 and 7.3 Hz, *meta*-H), 7.32—7.54 (5H, m, aromatic-H of N-Ph). *Anal.* Calcd for $C_{16}H_{13}CrNO_3$: C, 60.19; H, 4.10; N, 4.39. Found: C, 60.16; H, 4.21; N, 4.28.

π-(*N*-Ethyl-*N*-phenylaniline)chromium Tricarbonyl (5e)——In the same manner as described above, but using *N*-ethylaniline in this case, **5e** was obtained as a yellow powder in 70% yield. Recrystallization from ether–hexane gave yellow prisms of mp 124—125 °C. IR ν_{max}^{Nujol} cm^{-1}: 1940, 1855, 1835 (C≡O), 1595, 1580 (Ar), 1535 (Ar-N). NMR (d_6-acetone) δ: 1.22 (3H, t, *J*=7.1 Hz, N-$CH_2\underline{C}H_3$), 3.70 (2H, q, *J*=7.1 Hz, N-$C\underline{H}_2CH_3$), 4.94 (2H, d, *J*=6.6 Hz, *ortho*-H), 4.99 (1H, t, *J*=6.4 Hz, *para*-H), 5.80 (2H, dd, *J*=6.4 and 7.3 Hz, *meta*-H), 7.33—7.57 (5H, m, aromatic-H of N-Ph). *Anal.* Calcd for $C_{17}H_{15}CrNO_3$: C, 61.26; H, 4.53; N, 4.20. Found: C, 61.23; H, 4.56; N, 4.19.

π-(*N*,*N*-Diphenylaniline)chromium Tricarbonyl (5f)——In the same manner as for **5d**, using diphenylamine in this case, **5f** was obtained as a yellow powder in 74% yield. Recrystallization from CH_2Cl_2–ether–hexane gave yellow needles of mp 155 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1940, 1850 (C≡O), 1590, 1585 (Ar), 1530 (Ar-N). NMR (d_6-acetone) δ: 4.96 (2H, d, *J*=7.3 Hz, *ortho*-H), 5.10 (1H, t, *J*=6.4 Hz, *para*-H) 5.81 (2H, dd, *J*=6.4 and 7.3 Hz, *meta*-H), 7.32—7.53 (10H, m, aromatic-H of N-Ph). *Anal.* Calcd for $C_{21}H_{15}CrNO_3$: C, 66.14; H, 3.96; N, 3.67. Found: C, 65.97; H, 3.92; N, 3.66.

3-α-Hydroxybenzyl-*N*,*N*-dimethylaniline (6a-*meta*) and Its Isomers (6a-*ortho* and 6a-*para*)——π-(*N*,*N*-Dimethylaniline)chromium tricarbonyl (**5a**) (700 mg; prepared according to Nicholls' method[7]) was subjected to a series of reactions [lithiation (method A), PhCHO addition, and decomplexation with iodine] in the same manner as described for **4a**. The crude product was purified by silica gel chromatography to give **6a**-*ortho* (167 mg) and a mixture of **6a**-*meta* and **6a**-*para* (364 mg). The *ortho* isomer was recrystallized from ether–hexane to give colorless prisms of mp 68—70 °C, which were identical with an authentic sample derived from 2-aminobenzophenone. The isomeric mixture of **6a**-*meta* and **6a**-*para* was also recrystallized from ether–hexane to give colorless needles of mp 99—100 °C, which were identical with an authentic sample derived from 3-aminobenzyl alcohol. The retention time of the *para* isomer on gas chromatography was identical with that of an authentic sample derived from 4-(*N*,*N*-dimethylamino)benzaldehyde. The yield and the ratio of isomers are shown in Table II and physical properties are listed in Table IV.

TABLE IV. *N*, *N*-Disubstituted Aniline Derivatives (**6**)

Compd.	IR ν_{max}^{neat} cm^{-1} [a]	NMR (CCl_4) δ	MS *m/e*
6a-*ortho*	3330, 1590	2,55 (6H, s, NCH_3), 5.80 (1H, s, C<u>H</u>-Ph), 5.88 (1H, s, OH).	
6a-*meta*	3375, 1605, 1580	1.92 (1H, s, OH), 2.92 (6H, s, NCH_3), 5.60 (1H, s, C<u>H</u>-Ph)	
6b-*ortho*	3350, 1600, 1575	0.94 (9H, s, *tert*-Bu), 2.53 (3H, s, NCH_3), 2.83 (2H, s, C<u>H</u>$_2$-Bu-*tert*), 5.22 (1H, br, OH), 6.06 (1H, s, C<u>H</u>-Ph).	283 (M^+), 226 (M^+-Bu-*tert*, 100 %), 196, 91.
6b-*meta*	3350, 1600, 1575	0.94 (9H, s, *tert*-Bu), 2.04 (1H, s, OH), 2.94 (3H, s, NCH_3), 3.08 (2H, s, C<u>H</u>$_2$-Bu-*tert*), 5.57 (1H, s, C<u>H</u>-Ph).	283 (M^+), 226 (M^+-Bu-*tert*, 100%).
6c-*meta*	3400, 1600, 1575	[b] 0.92 (9H, s, *tert*-Bu), 1.05 (3H, t, *J*=6.8 Hz, $CH_2C\underline{H}_3$), 2.19 (1H, d, *J*=3.6 Hz, OH), 3.03 (2H, s, C<u>H</u>$_2$-Bu-*tret*), 3.39 (2H, q, *J*=6.8 Hz, $C\underline{H}_2CH_3$), 5.76 (1H, d, *J*=3.6 Hz, C<u>H</u>-Ph).	297 (M^+), 240 (M^+-Bu-*tert*, 100 %).
6d-*ortho*	3400, 1590, 1570	[b] 2.50 (1H, br, OH), 2.89 (3H, s, NCH_3), 5.92 (1H, s, CH-Ph).	289 (M^+), 270 (100 %), 194.
6d-*meta*	3400, 1590	2.10 (1H, s, OH), 3.28 (3H, s, NCH_3), 5.56 (1H, s, C<u>H</u>-Ph).	289 (M^+), 184.
6e-*ortho*	3400, 1570	[b] 1.13 (3H, t, *J*=7.1 Hz, $CH_2C\underline{H}_3$), 2.20 (1H, br, OH), 3.43 (2H, q, *J*=7.1 Hz, $C\underline{H}_2CH_3$), 5.92 (1H, br s, C<u>H</u>-Ph).	303 (M^+), 284 (100%), 256, 208.
6e-*meta*	3400, 1590	[b] 1.19 (3H, t, *J*=7.1 Hz, $CH_2C\underline{H}_3$), 2.20 (1H, br, OH), 3.76 (2H, q, *J*=7.1 Hz, $C\underline{H}_2CH_3$), 5.75 (1H, s, C<u>H</u>-Ph).	303 (M^+), 288 (M^+-CH_3, 100%).
6f-*meta*	3400, 1585	[b] 2.20 (1H, d, *J*=3.2 Hz, OH), 5.17 (1H, d, *J*=2.7 Hz, C<u>H</u>-Ph).	351 (M^+, 100%).

a) Nujol mulls were used for **6a**-*ortho* and **6a**-*meta*.
b) In $CDCl_3$.

3-α-Hydroxybenzyl-*N*-methyl-*N*-neopentylaniline (6b-*meta*) and Its Isomers (6b-*ortho* and 6b-*para*)——**5b** (1.0 g) was subjected to a series of reactions [lithiation (method A), PhCHO addition, and decomplexation with iodine] in the same manner as described for **4a**. The crude product was purified by silica gel chromatography to give 668 mg of a colorless oil as an isomeric mixture, which was analyzed by gas chromatography. *Ortho* and *meta* isomers were respectively obtained by medium pressure liquid chromatography using a Lobar column. The corresponding *para* isomer could not be isolated, but was detected by gas chromatography and GC–MS. The yield and the ratio of isomers are shown in Table II and physical properties are listed in Table IV.

***N*-Ethyl-3-α-hydroxybenzyl-*N*-neopentylaniline (6c)**——**5c** (1.0 g) was subjected to a series of reactions [lithiation (method A), PhCHO addition, and decomplexation with iodine] in the same manner as described for **4a**. The crude product was purified by silica gel chromatography to give 579 mg of a colorless oil, which was analyzed by gas chromatography. The yield and the ratio of isomers are shown in Table II and physical properties are listed in Table IV.

3-α-Hydroxybenzyl-*N*-methyl-*N*-neopentylaniline (6d-*meta*) and Its *ortho* Isomer (6d-*ortho*)——**5d** (1.0 g) was subjected to a series of reactions [lithiation (method A), PhCHO addition, and decomplexation with iodine] in the same manner as described for **4a**. After iodine treatment of the reaction mixture, 40% $NaHSO_3$ was added and the whole was immediately made alkaline by the addition of 20% NaOH, then extracted with ether. The extract was dried over Na_2SO_4 and concentrated to give a yellow oil, which was acetylated with Ac_2O/Py. The crude acetate was chromatographed on silica gel with EtOAc–hexane (1:9) as an eluent to give the *ortho* isomer, *meta* isomer, and a mixture of the two (total 968 mg). The fractions were each treated with 10% KOH/MeOH and purified again by silica gel chromatography using EtOAc–hexane (1:4) as an eluent to give the 2-α-hydroxybenzyl and 3-α-hydroxybenzyl derivatives and a mixture of the two (total 576 mg, overall 64% yield). In this case, the *para* isomer was not detected even by GC–MS analysis. The ratio of isomers is shown in Table II and physical properties are listed in Table IV.

***N*-Ethyl-3-α-hydroxybenzyl-*N*-phenylaniline (6e-*meta*) and Its *ortho* Isomer (6e-*ortho*)**——In the same manner as described above, **6e**-*ortho*, **6e**-*meta*, and a mixture of the two were obtained. In this case too, the *para* isomer was not detected even by GC–MS analysis. The yield and the ratio of isomers are shown in Table II and physical properties are listed in Table IV.

3-α-Hydroxybenzyl-*N*,*N*-diphenylaniline (6f)——In the same manner as described for **6d**, **6f** was obtained as a yellowish oil in 75% yield. The corresponding *ortho* and *para* isomers were not detected by GC–MS analysis. Physical properties are listed in Table IV.

π-(*tert*-Butyldimethylsilyloxybenzene)chromium Tricarbonyl (7a)——A mixture of phenol (20 g), $Cr(CO)_6$ (20 g), and decalin (100 ml) was heated under reflux (bath temp.; 185—190 °C) for 6 h under one atmosphere pressure of argon.[7] $Cr(CO)_6$ that sublimed on the inside of the reflux condenser was continually returned mechanically to the reaction flask. After cooling, phenol, $Cr(CO)_6$, and decalin were removed under reduced pressure [13.2 g of unreacted $Cr(CO)_6$ was recovered] to give crystalline solids, which were washed with hexane. The resulting yellow powder (5 g) was dissolved in DMF (14 ml). *tert*-$BuMe_2SiCl$ (3.9 g) and imidazole (3.7 g) were added to this solution and the whole was stirred overnight at room temperature. The reaction solution was diluted with ether, washed with water 4 times, and dried over Na_2SO_4. The solvent was removed to give a yellow oil, which was chromatographed on silica gel. Elution with CH_2Cl_2–hexane (1:2) gave 3.8 g of **7a** as a yellow solid [36% yield, calculated from the consumed $Cr(CO)_6$]. Recrystallization from ether–hexane gave yellow prisms of mp 74—75 °C. IR ν_{max}^{Nujol} cm^{-1}: 1980, 1960, 1905, 1880 (C≡O), 1520 (Ar–O). NMR (d_6-acetone) δ: 0.34 (6H, s, Si-CH_3), 0.98 (9H, s, Si-Bu-*tert*), 5.06 (1H, t, *J*=6.6 Hz, *para*-H), 5.33 (2H, d, *J*=6.6 Hz, *ortho*-H), 5.79 (2H, t, *J*=6.6 Hz, *meta*-H). *Anal.* Calcd for $C_{15}H_{20}CrO_4Si$: C, 52.31; H, 5.85. Found: C, 52.38; H, 5.89.

π-(*tert*-Butyldiphenylsilyloxybenzene)chromium Tricarbonyl (7b)——π-(Phenol)chromium tricarbonyl (1.967 g) prepared in the same manner as described above was treated with *tert*-$BuPh_2SiCl$ (4.43 ml) and imidazole (1.745 g) in DMF (5 ml) for 1 h at 0 °C, and the resulting crude product was purified on a Lobar column using ether–hexane (1:4) as an eluent to give 1.933 g of a yellow solid (48% yield). Recrystallization from ether–hexane gave yellow needles of mp 101—102 °C. IR ν_{max}^{Nujol} cm^{-1}: 1965, 1890, 1870 (C≡O), 1585 (Ar), 1520 (Ar–O). NMR (d_6-acetone) δ: 1.11 (9H, s, Si-Bu-*tert*), 5.06 (1H, t, *J*=6.4 Hz, *para*-H), 5.24 (2H, dd, *J*=7.1 and 1.0 Hz, *ortho*-H), 5.68 (2H, dd, *J*= 7.1 and 6.4 Hz, *meta*-H), 7.46—7.81 (10H, m, aromatic-H of Si-Ph). *Anal.* Calcd for $C_{25}H_{24}CrO_4Si$: C, 64.09; H, 5.16. Found: C, 64.12; H, 5.14.

2-*tert*-Butyldimethylsilylphenol (8a) and 3-α-Hydroxybenzylphenol (9)——**7a** (1.5 g) was subjected to a series of reactions [lithiation (method A), PhCHO addition, and decomplexation with iodine] in the same manner as described for **4a**. After iodine treatment followed by addition of 40% $NaHSO_3$, the mixture was extracted with ether. The ether layer was extracted with 10% NaOH and then dried over Na_2SO_4. The solvent was removed to give a yellow oil, which was chromatographed on silica gel with ether–hexane (1:9) as an eluent to give **8a** as a white solid (320 mg, 35%) of 62—64 °C. IR ν_{max}^{Nujol} cm^{-1}: 3500 (OH), 1585, 1565 (Ar). NMR (CCl_4) δ: 0.32 (6H, s, Si-CH_3), 0.94 (9H, s, Si-Bu-*tert*), 4.80 (1H, br s, OH). MS *m/e*: 208 (M^+), 151 (M^+–Bu-*tert*, 100%). **8a** was methylated with MeI in refluxing acetone in the presence of K_2CO_3 to afford 2-*tert*-butyldimethylsilylanisole as a colorless oil, which was identical with an authentic sample prepared by the

reaction of 2-lithioanisole with *tert*-BuMe$_2$SiCl. IR ν_{max}^{Nujol} cm^{-1}: 1590, 1570 (Ar). NMR (CCl_4) δ: 0.27 (6H, s, Si-CH_3), 0.88 (9H, s, Si-Bu-*tert*), 3.63 (3H, s, OCH_3). MS *m/e*: 222 (M^+), 165 (M^+–Bu-*tert*, 100%), 135. The alkaline extract mentioned above was acidified with cold conc. HCl and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated to give a yellow oil, which was chromatographed on silica gel. Elution with EtOAc–hexane (1:2) gave 345 mg (40%) of **9** as a white solid, which was recrystallized from ether–hexane to afford colorless prisms of mp 149—150 °C. **9** was identical with an authentic sample derived from 3-hydroxybenzaldehyde. IR ν_{max}^{Nujol} cm^{-1}: 3350(OH), 3075 (br, phenol), 1590 (Ar). NMR ($CDCl_3$) δ: 2.22 (1H, d, J=3.4 Hz, CH-O<u>H</u>), 4.86 (1H, s, Ph-OH), 5.80 (1H, d, J=3.4 Hz, C<u>H</u>-OH). *Anal.* Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.70; H, 6.16.

When π-(*tert*-butyldiphenylsilyloxybenzene)chromium tricarbonyl (**7b**) was subjected to the series of reactions described above, 2-*tert*-butyldiphenylsilylphenol (**8b**) and **9** were obtained in 19% and 48% yields, respectively. **8b**: white crystals (from ether–hexane), mp 190—191 °C. IR ν_{max}^{Nujol} cm^{-1}: 3530 (OH), 1585, 1565 (Ar). NMR ($CDCl_3$) δ: 1.21 (9H, s, Si-Bu-*tert*), 4.93 (1H, s, OH). MS *m/e*: 275 (M^+–Bu-*tert*, 100%), 257, 197. *Anal.* Calcd for $C_{22}H_{24}OSi$: C, 79.47; H, 7.27. Found: C, 79.06; H, 7.46.

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10) Crystal data: crystals of $C_{16}H_{23}CrNO_3Si$ (**3**) are triclinic, space group $P\bar{1}$ with a=7.368(3), b=19.218(5), c=7.316(3)Å, α=93.55(3), β=119.69(2), γ=88.67(3)°; V=898.2 Å^3; Z=2 and D_{calcd}=1.322 g/cm^3. X-Ray diffraction data were measured on Rigaku AFC four-circle diffractometer with graphite-monochromated Mo$K\alpha$ radiation. Within the range $2\theta \leq 55°$, 2422 independent reflections with $|F| \geq 3\sigma(F)$ were observed. The structure was solved by the heavy atom method, and was refined by the block-diagonal least-squares method. All atoms were located from the difference Fourier map, and were included in the refinement with isotropic temperature factors. The final R factor was 3.2%. Final atomic parameters and anisotropic temperature factors have been deposited with the Cambridge Crystallographic Data Centre.

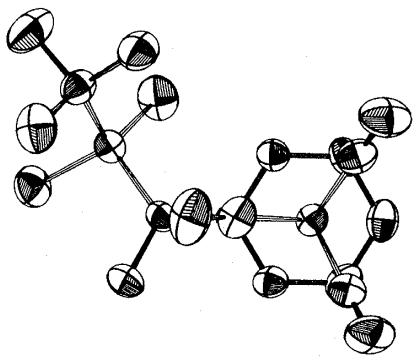

Chart 6

11) The X-ray analysis was carried out by Dr. Toshio Sakurai and Miss Kimiko Kobayashi of this Institute. We are indebted to them for their expert assistance.
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14) The bulkiness of substituents on the nitrogen atom should also affect the *meta*/*para* ratio, since π-(*N*,*N*-dimethylaniline)chromium tricarbonyl (**5a**) gives very unsatisfactory results (Table II, entry 1).