Product Isomer Analysis. The ratio of **8** to **9** was determined by comparison of the integrated intensities of selected bands (specifically, those corresponding to the $-CH_2Fe$ and $CH_2{=}CH-$ protons) in the ^1H NMR spectrum of the product mixtures isolated as described above.

Acknowledgments. The authors are indebted to Ms. Myrna L. Hagedorn for extensive assistance in obtaining and interpreting the ^{13}C NMR spectra, and to Mr. Ybette Villacorta for his technical assistance in several instances.

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Aminohaloborane in Organic Synthesis. 1. Specific Ortho Substitution Reaction of Anilines[1]

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Abstract: A new general process has been developed for specific ortho hydroxybenzylation and hydroxyalkylation of secondary anilines using secondary anilinodichloroboranes. Treatment of secondary anilinodichloroborane prepared in situ with benzaldehydes in the presence of tertiary amines with some steric hindrance gave secondary 2-(α-hydroxybenzyl)anilines in excellent yield via the cyclic transition state; in contrast, the analogous treatment with anilinodichloroalane proceeded intermolecularly affording 4,4′-diaminotriphenylmethane exclusively. Similarly, a new general process was developed for specific ortho acylation of anilines by the reaction of nitriles and anilinodichloroborane prepared in situ. This reaction was accelerated in most cases by the coexistence of aluminum trichloride. The distinctive exchange of the reaction site of anilines and nitriles in the presence of boron trichloride instead of other electrophilic metal halides is discussed.

2-Aminophenyl ketones (**1**), such as 2-aminobenzophenone (**1a**) and 2-aminoacetophenone (**1b**) and their substituted derivatives, have been used for a long time as important starting materials for the preparation of fluorenones,[2] acridines and acridones,[2,3] cinnolines,[2,4] quinazolines,[2,5] indazoles,[2,6] and quinolines.[7] Recently, use of 2-aminobenzophenones for the preparation of 3-phenylindoles[8] has been also reported. Among the various synthetic uses of these 2-aminobenzophenones (**1a**), their use in preparing 1,4-benzodiazepines[9] (**2**), which have become among the most important drugs in the clinical field of psychosis, is the most outstanding.

In spite of their versatility as reactive intermediates, a simple preparative route to **1** from anilines has not been known to date because the Friedel-Crafts acylation of anilines is usually unsuccessful and the same reaction of acylanilides with acyl halides gives 4-substituted acylanilides almost exclusively.[10] Also, the reaction of anilines with various acylating agents such as benzamide, benzonitrile, ethyl benzoate and benzoic acid in the presence of polyphosphoric acid gives only 4-aminobenzophenone.[11]

Consequently, the known synthetic routes to **1** involve three or four steps starting from 1,2-disubstituted benzene derivatives. Namely, treatment of 2-nitrobenzoyl chloride or 2-nitrobenzyl chloride with benzene derivatives in the presence of aluminum chloride followed by further appropriate treatment or the Grignard reaction of 1,3-benzoxazin-4-one or 2-aminobenzonitrile gives the desired product **1**.[2,12] Other minor synthetic routes are also reviewed in the same literature. Alternatively, the Friedel-Crafts reaction of phthalic anhydride with benzene followed by amidation and Hofmann degradation[13] or the oxidative cleavage of 3-substituted indoles[14] and subsequent hydrolysis gives **1**. Of course, there is no re-

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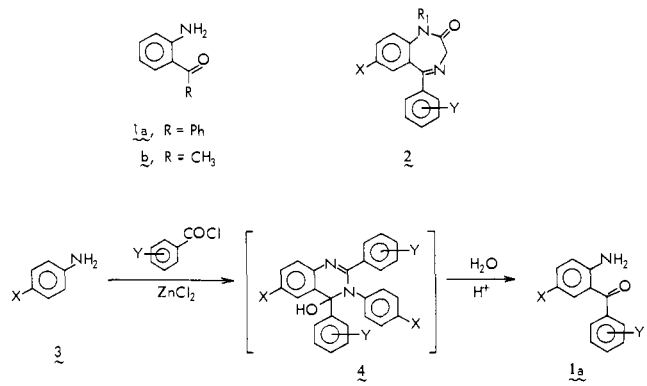
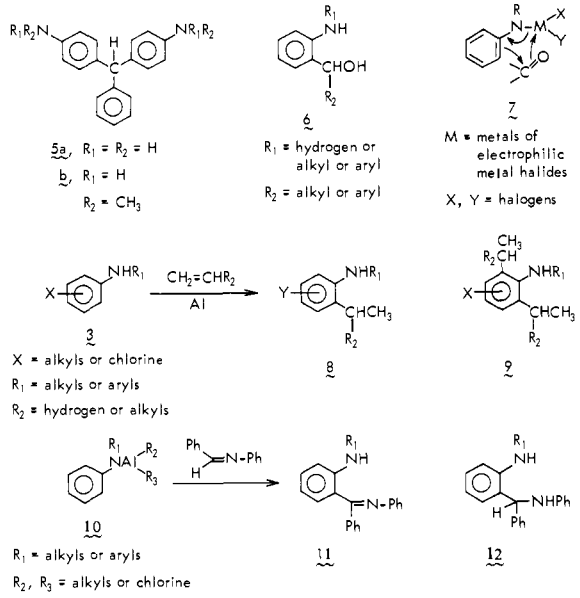
Scheme I



Scheme II



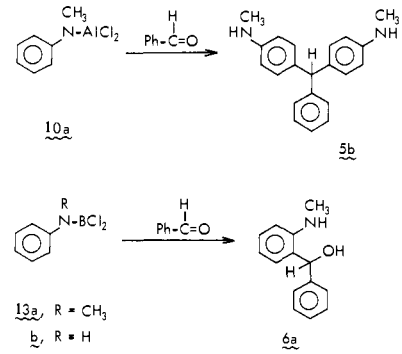
giospecific problem when the Friedel-Crafts reaction is used in preparing the starting materials for **2,** because only 4-substituted (mainly chloro or nitro) anilines are used. However, the reaction conditions are very drastic; namely, heating of 4-substituted anilines with benzoyl chlorides in the presence of zinc chloride at 200 to 230 °C and the subsequent energetic hydrolysis of the intermediate **4** must be carried out.[15]

Similarly, the synthetic methodology of specific ortho hydroxybenzylation and hydroxyalkylation of primary and secondary anilines[16] is also completely unknown to date. The reaction of aniline with benzaldehyde under strong acidic conditions with or without zinc chloride takes place at the para position of aniline, giving 4,4′-diaminotriphenylmethane (**5a**).[17] Therefore, the following reaction sequences are used, for example, when 2-(α-hydroxybenzyl)aniline (**6**) (R_1 = H or alkyls; R_2 = aryls) are prepared. Namely, reduction of 2-aminobenzophenones, which are prepared by three- or four-step synthetic sequences stated above or by Grignard reaction of 2-nitrobenzaldehydes, and then reduction of the nitro group[18] are necessary.

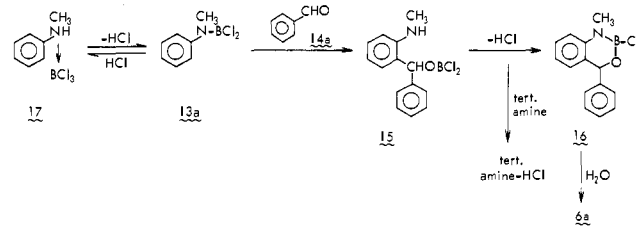
In order to find a one-step synthesis for the compound **6** series, we first tried a specific ortho hydroxybenzylation of *N*-methylaniline to obtain *N*-methyl-2-(α-hydroxybenzyl)-aniline (**6a**) ($R_1 = CH_3$; $R_2 = C_6H_5$). To accomplish this, a reaction which proceeds through a cyclic transition state as depicted in **7** seemed attractive.

Using a similar idea, Ecke and Stroh succeeded independently in obtaining 2-alkyl- and 2,2′-dialkylanilines (**8, 9**) from anilines and olefines in the presence of a catalytic amount of aluminum under high temperature and pressure.[19] Recently,

Scheme III



Scheme IV



Hoberg reported a successful reaction giving 2-aminobenzophenone imines (**11**) and 2-aminobenzylanilines (**12**) from anilinoalanes (**10**) with *N*-benzylideneanilines.[20]

Results and Discussion

Our initial attempt to obtain **6a** ($R_1 = CH_3$; $R_2 = C_6H_5$) by a reaction using *N*-methylanilinodichloroalane (**10a**) ($R_1 = CH_3$; $R_2 = R_3 = Cl$)[20] and benzaldehyde gave only para-substituted triphenylmethane (**5b**) (66%), suggesting, contrary to expectation, an intermolecular pathway like the known reaction of reference 17.

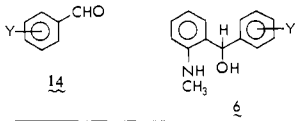
As the next candidate, *N*-methylanilinodichloroborane (**13a**), readily prepared from *N*-methylaniline (**3a**) (X = H; $R_1 = CH_3$) and boron trichloride,[21] was chosen with the expectation of a stronger Lewis acidity for **13a** than **10a.** Actually, the reaction of **13a** with benzaldehyde in dichloromethane under ice cooling for 30 min to 2 h gave the desired product **6a** (26%) without coformation of **5b,** showing a clear distinction in the reaction site which undoubtedly resulted from the cyclic transition state shown in **7** (R = CH_3; M = B; X = Y = Cl). Besides **6a,** only unchanged starting material was recovered. When this reaction was carried out in refluxing dichloroethane, **5b** and **6a** were produced in the ratio of 1:2 according to estimation of the NMR spectrum. Besides **5b** and **6a,** more than 50% of the starting materials were recovered, according to the thin-layer chromatogram.

The reaction of **13a** with substituted benzaldehydes (**14**) proceeded analogously as shown in Table I. Again, only the starting materials were isolated besides the desired products.

The structures of the products were characterized by direct comparison with an authentic sample (**6a**)[22] or by elemental analyses and their reasonable IR (OH and NH signals at ca. 3600 and 3430 cm^{-1}) and NMR spectra (one benzyl proton at ca. 6 ppm and complicated ABCD pattern of aniline ring protons) (**6b–d**). The oily product **6e** was converted to its crystalline *p*-dinitrobenzoate and then characterized.

The reaction pathway proposed is: **13a** reacts with **14a** via the expected transition state, giving the primary product **15** which changes to **16** by dehydrochlorination. The resulting hydrogen chloride, which may convert the reaction species **13a** into the inactive species **17,** is thought to be responsible for the moderate yield of this reaction, as noted in Table I. In support of this assumption, addition of 1 molar equiv of tertiary amine, such as tri-*n*-butylamine, to trap the hydrogen chloride raised

Table I. Yields of *N*-Methylamino-2-(α-hydroxybenzyl)anilines (**6**) in the Reaction of *N*-Methylanilinodichloroborane (**13a**) and Benzaldehydes (**14**)



run	compd	Y	compd	% yield
1	**14a**	H	**6a**	26 (81)[a]
2	**14b**	2-Cl	**6b**	33
3	**14c**	2-NO_2	**6c**	32 (97)
4	**14d**	4-NO_2	**6d**	47 (79)
5	**14e**	4-OCH_3	**6e**	38 (84)

[a] Values in parentheses indicate the yield of **6** obtained in the presence of $(n\text{-Bu})_3N$.

the yield significantly, as shown by the values in parentheses in Table I.

Here we examined the influence of tertiary amines on the product **6a** yield. As can be noted from Table II, the yield in the run with pyridine (**18**) was much poorer than that with 2,6-lutidine (**19**). This remarkable difference can be rationalized by assuming that **18** forms a much more stable complex with **13a** than **19** does. This assumption is based on the $-\Delta H$ thermodynamic values of trimethylborane complexes of both amines. The **19**-trimethylborane complex is considered to be unstable due to "F strain" of the base as suggested by Brown.[23] Whereas the comparatively stable **13a–18** complex possesses very poor Lewis acidity for reaction with benzaldehyde (**14a**), the unstable **13a–19** complex may dissociate or have Lewis acidity sufficient to form the transient **13a–14a** complex under ligand exchange. Moreover, **19** can scavange the liberating hydrogen chloride. The similar but less distinct difference in the yield between the runs with trimethylamine (**20**) and triethylamine (**21**) can be interpreted analogously from the different stabilities of the **13a–20** and **13a–21** complexes arising from a bigger F strain of **21**. Thus, tertiary amines which poorly coordinate with **13a**, but can trap hydrogen chloride, are favorable. Diisopropylethylamine (**22**), tri-*n*-butylamine (**23**), and dimethylaniline (**24**) satisfy these criteria as shown in Table II.

Next, the use of other solvents was tested. As shown in Table III, changing the solvents had no substantial influence on the yield of **6a**.

Practically, the operation can be performed as a "one-pot reaction"; namely, a solution of an *N*-methylaniline derivative **3** and boron trichloride in dichloroethane or benzene is refluxed for 1 to 2 h under nitrogen to obtain a solution containing a derivative of **13a**, to which a solution of **14** and 1 to 2 molar equiv of **21** or **23** is added under ice cooling and stirring at ice to room temperature for 0.5 to a few hours. The reaction seems to be completed almost spontaneously according to monitoring by thin-layer chromatogram. Table IV shows various examples.

The structure of **6** was proved by corresponding physical data like the products in Table I.

Even weakly basic 4-nitroaniline (**3c**) reacted with benzaldehydes giving good to excellent yields (**6j** and **k**) as can be noted from Table IV. The yields from 4-chloro-*N*-diethylaminoethylaniline (**3d**) was quite good (**61**). In the case of *N*-methylaniline containing an acid-labile substituent like the carboalkoxy group (**3e**), a mixed solution of the substrate, boron trichloride, benzaldehyde, and more than 2 molar equiv of **21** in dichloromethane was stirred at ice to room temperature for a few hours giving **6m**. The reaction of 3-chloro-*N*-methylaniline (**3f**) gave two products, namely, 2,3- and 2,5-disubstituted anilines (**6n** and **6o**).

Table II. Influence of Tertiary Amines on Yields of *N*-Methyl-2-(α-hydroxybenzyl)aniline (**6a**)

run	tertiary amine	pK_a[a]	K_{100}[b]	$-\Delta H$[b]	solvent	% yield
1	**18**	5.25	0.301	15.3	CH_2Cl_2	24
2	**19**	6.60		<0	CH_2Cl_2	88
3	**20**	9.98	0.472		Ph-H	45
4	**21**	11.01	unstable		Ph-H	85
5	**22**				CH_2Cl_2	86
6	**23**	9.93			Ph-H	85
7	**24**	5.12			CH_2Cl_2	73

[a] D. D. Perrin, "Dissociation Constant of Organic Base in Aqueous Solution", London, Butterworth, 1965. [b] K_{100}: dissociation constant of tertiary amine-trimethylborane complex in the gaseous phase. ΔH: heat of reaction of tertiary amines with trimethylborane at 25 °C in nitrobenzene solution. See reference 23.

Table III. Influence of Solvent on the Yield of *N*-Methyl-2-(α-hydroxybenzyl)aniline (**6a**)

solvent	% yield
Dichloromethane	81
Benzene	85
Acetonitrile	80
DMF-dichloromethane (4:3)	83
Tetrahydrofuran	84

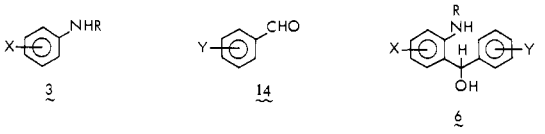
Attempts to apply this reaction to aliphatic aldehydes or ketones were less satisfactory, giving the corresponding *N*-methyl-2-(α-hydroxyalkyl)aniline (**26**) in the poor to moderate yields shown in Table V. This may be attributed to the enolizable carbonyl substrates.

As described above, our method can be successfully applied to secondary anilines and aromatic aldehydes bearing electron-withdrawing and electron-releasing substituents. But when substituents (Cl or OCH_3) are situated ortho to the amino function on the aniline ring, the reaction with **14** does not proceed. This may be attributed to a reduced Lewis acidity of the intermediate based on the coordination of the substituents. Moreover, attempts to apply this reaction to aniline have failed, giving mainly benzylideneaniline and only traces of the desired **6** (R_1 = H; R_2 = C_6H_5). The poor result may be due to the unstable anilinodichloroborane (**13b**) and the rapid formation of benzylideneaniline.

In this way, anilinodichloroboranes (**13** with or without substituents) proved to be useful intermediates for realizing the specific ortho carbon-carbon bond formation on the aniline ring, though their use was accompanied by some limitations. Next, we tried the reaction of **13** with nitriles in order to perform a one-step synthesis of **1** directly from **3**.

In line with expectations, treatment of aniline with benzonitrile (**28a** R_2 = Ph) in the presence of boron trichloride in refluxing benzene followed by acidic hydrolysis of the resulting imine **29a** gave the desired product **1a**[13] in 18% yield. From the basic fraction of the reaction mixture *N*-phenylbenzamidine (**30a**),[25] was isolated in 3% yield besides recovered aniline (ca. 70%) (Table VI, run 1). **30a** might be formed via the transition state **27** represented by the dotted arrows. In support of the supposed reaction path (the solid arrows) depicted in **27**, no 4-aminobenzophenone was detected. When the above reaction was carried out in refluxing tetrachloroethane, the yield of **1a** did not improve (17%); however, **30a** was isolated in a comparable yield (14%) (Table VI, run 2). Besides recovered aniline (ca. 60%), a small amount of a neutral product was isolated; its structure was not elucidated. Again, no 4-aminobenzophenone could be found. Apart from the ortho-para regiospecificity on the aniline ring, it is very remarkable that the above reaction of aniline and **28a** in the presence of boron trichloride gave **1a**, albeit in modest yield, as the main product,

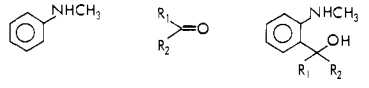
Table IV. Synthesis of Secondary 2-(α-Hydroxybenzyl)anilines (**6**) from Secondary Anilines (**3**) and Benzaldehydes (**14**)



run	compd	R	X	compd	Y	solvent[a]	compd	% yield
1	**3a**	CH_3	H	**14a**	H	B	**6a**[22]	84
2	**3a**	CH_3	H	**14h**	4-$COOCH_3$	B	**6f**	88
3	**3b**	CH_3	4-Cl	**14a**	H	DCE	**6g**[24]	88 (68)[b]
4	**3b**	CH_3	4-Cl	**14b**	2-Cl	B	**6h**	87
5	**3b**	CH_3	4-Cl	**14g**	3,4,5-$(OCH_3)_3$	B	**6i**	74
6	**3c**	CH_3	4-NO_2	**14b**	2-Cl	DCE	**6j**	84
7	**3c**	CH_3	4-NO_2	**14g**	3,4,5-$(OCH_3)_3$	DCE	**6k**	71
8	**3d**	$(C_2H_5)_2NCH_2CH_2$	4-Cl	**14i**	2-F	DCE	**6l**	81
9	**3e**	CH_3	4-$COOC_2H_5$	**14a**	H	B	**6m**	69
10	**3f**	CH_3	3-Cl	**14a**	H	DCE	**6n**	65
							6o	19

[a] B, benzene; DCE, dichloroethane. [b] Yield in the reaction using boron tribromide instead of boron trichloride.

Table V. Synthesis of *N*-Methyl-2-(α-hydroxyalkyl)anilines (**26**) from *N*-Methylaniline (**3a**) and Aliphatic Carbonyl Compounds (**25**)



compd	compd	R_1	R_2	compd	% yield
3a	**25a**	*n*-C_3H_7	H	**26a**	38
3a	**25b**	CH_3	CH_3	**26b**	8

Scheme V

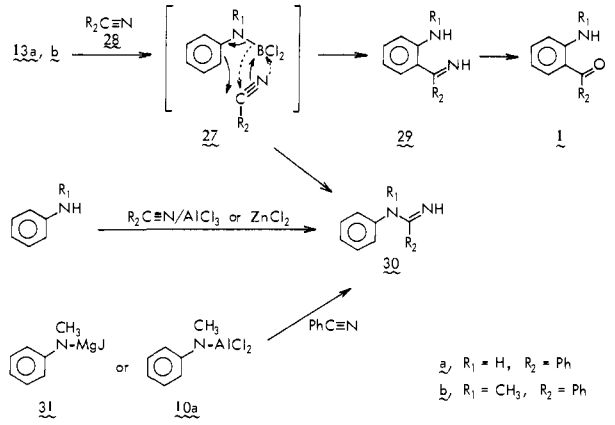
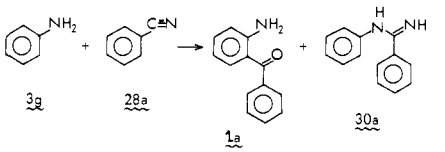


Table VI. Yields of 2-Aminobenzophenone (**1a**) and *N*-Phenylbenzamidine (**30a**) in the Reaction of Aniline (**3g**) and Benzonitrile (**28a**) in the Presence of Boron Trichloride with or without Additional Lewis Acids



run[a]	solvent[b]	additional Lewis acid[c]	% yield[d] of **1a**	% yield of **30a**[e]
1	B	none	18	3
2	TCE	none	17	14
3	B	BCl_3	7	tr
4	B	$AlCl_3$	50	tr
5	X	$AlCl_3$	49	6
6	DCE	$AlCl_3$	63	1
7	TCE	$AlCl_3$	59	6
8	B	$TiCl_4$	3	tr
9	B	$ZnCl_2$	23	2
10	B	$SnCl_4$	21	7

[a] In all runs, 1.1 equiv of boron trichloride based on aniline was used. In runs 5 and 6, 2 equiv of **28a** was used. Otherwise, 1.1 equiv of **28a** was used. In all runs except 7, the reactions were carried out for 6 h. In the run 7, it was carried out for 3 h. [b] B, benzene; TCE, tetrachloroethane; X, xylene; DCE, dichloroethane. [c] 1.1 equiv of additional Lewis acid to aniline was used. [d] Yield based on alinine used. [e] tr, trace

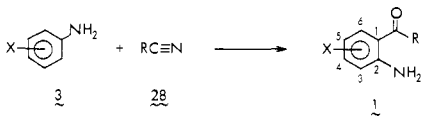
because a similar reaction in the presence of Lewis acids such as aluminum trichloride or zinc chloride is a general synthetic method for **30**.[25] *N*-Methylanilinomagnesium iodide[26] (**31**) or *N*-methylanilinoaluminum dichloride[27] (**10a**) reacts also with **28a** to give **30b** at room temperature.

In order to improve the yield of **1a**, the influence of the coexistence of additional Lewis acid was tested as shown in runs 3 to 10 of Table VI. Namely, the presence of additional boron trichloride gave a poorer result (run 3), but as can be noted from runs 4 to 7 the coexistence of additional aluminum trichloride raised the yield of **1a** significantly. Note further that the addition of aluminum trichloride suppressed the yield of **30a**. Other Lewis acids, such as titanium tetrachloride, zinc chloride, or stannic tetrachloride, were not effective (runs 8-10).

Clearly, changing the reaction site of aniline from the nitrogen to the carbon atom situated ortho to the amine function with the electrophilic center of benzonitrile could be performed in the presence of boron trichloride with the cooperation of aluminum trichloride. As shown in Table VII, this reaction was generally applicable to substituted anilines and aromatic or aliphatic nitriles.

In a typical procedure, to a stirred solution of 1 to 1.1 equiv of boron trichloride in an appropriate solvent was added 1 equiv of an aniline under ice cooling. To the resulting aniline-boron trichloride complex, 1 to 2 equiv of nitrile and 1 to 1.1 equiv of aluminum trichloride were added successively. Within 10 min, both the aniline-boron trichloride complex and aluminum trichloride dissolved, and the solution was refluxed for the number of hours indicated in Table VII. Workup involving hydrolysis of a 2-aminophenylketimine (**29**) by warming with dilute hydrochloric acid gave the desired product **1** from the neutral fraction. From a thin-layer chromatogram of the basic fraction, a considerable amount (20-40%) of aniline was recovered. Therefore, the yield of **1** will amount to 60-90% based on the unrecovered aniline. Recovery of anilines can be explained as follows. While initially formed anilinodichloroborane (**13b**) reacted with **28** to give **1**, **13b** changed competitively

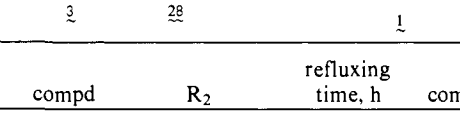
Table VII. Yields of 2-Aminophenyl Ketones (**1**) in the Reaction of Primary Anilines (**3**) and Nitriles (**28**) in the presence of Boron Trichloride with Additional Aluminum Trichloride



run[a]	compd	X	compd	R	solvent[b]	refluxing time, h	compd	X	% yield[c]
1	**3g**	H	**28b**	CH_3	B	15	**1b**[28a,b]	H	65
2	**3g**	H	**28c**	$PhCH_2$	DCE	20	**1c**[12,14b]	H	76
3	**3g**	H	**28d**	$ClCH_2$	DCE	3	**1d**[29]	H	52
4	**3h**	4-Cl	**28a**	Ph	TCE	6	**1e**[30]	5-Cl	42[d]
5	**3i**	2-Cl	**28a**	Ph	TCE	6	**1f**[15b]	3-Cl	48
6	**3j**	3-Cl	**28a**	Ph	TCE	6	**1g**[15b]	4-Cl	49
							1h[15b]	6-Cl	1
7	**3k**	4-OCH_3	**28a**	Ph	TCE	4	**1i**[15b]	5-OCH_3	44
8	**3j**	3-Cl	**28e**	$Cl(CH_2)_3$-	B	8	**1j**	4-Cl	67[e]

[a] Two equivalents of **28** based on **3** was used in runs 1 to 7 and 1.1 equiv of **28** in run 8. [b] For the abbreviations, see footnote *b* in Table VI. [c] Yield based on aniline used. [d] In this run 4-chloro-*N*-phenylbenzamidine[32] was isolated (15%), besides recovered **3b** (23%). In other runs, the formation of corresponding *N*-phenylbenzamidine was negligible. [e] Yield calculated from corresponding *N*-acetate.

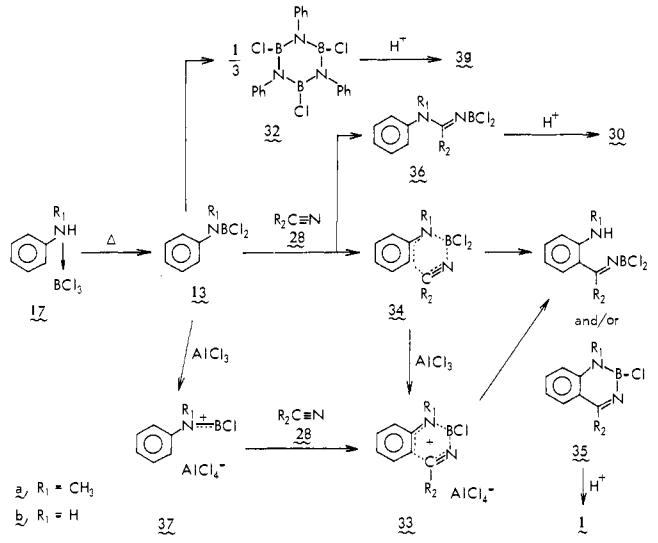
Table VIII. Synthesis of Secondary 2-Aminophenyl Ketones (**1**) from Secondary Anilines (**3**) and Nitriles (**28**)



run	compd	X	R_1	compd	R_2	refluxing time, h	compd	X	% yield[a] of method A[b]	B[c]	C[d]
1	**3a**	H	CH_3	**28a**	Ph	2,[e] 3[f]	**1k**[33]	H	43 (78)	61	87
2	**3a**	H	CH_3	**28e**	2-ClPh	6	**1l**	H	53 (88)		
3	**3a**	H	CH_3	**28g**	3-NO_2Ph	3	**1m**	H	56 (93)		
4	**3a**	H	CH_3	**28j**	C_2H_5	20	**1n**	H		79 (92)	
5	**3a**	H	CH_3	**28k**	$CH_3(CH_2)_3$	15	**1o**	H	25	65	
6	**3b**	4-Cl	CH_3	**28a**	Ph	5	**1p**[15b]	5-Cl	7 (23)	53 (93)	69
7	**3b**	4-Cl	CH_3	**28e**	2-ClPh	5	**1q**[15b]	5-Cl	29	40	61
8	**3c**	4-NO_2	CH_3	**28a**	Ph	17	**1r**[34]	5-NO_2			29 (32)
9	**3d**	4-Cl	$(CH_2)_2N(C_2H_5)_2$	**28a**	Ph	3	**1s**[35]	5-Cl		79	

[a] Yield based on secondary aniline used. Yields in parentheses were based on unrecovered secondary aniline. [b] Tetrachloroethane was used as the solvent in all runs. 1.1 equiv of the nitrile based on the aniline was used in all runs except run 5. In run 5, 2 equiv of valeronitrile was used. [c] Tetracholoroethane was used as the solvent in runs 1, 6, 7, and 9. Benzene was used as the solvent in runs 4 and 5. 1.1 equiv of the nitrile based on the aniline was used in all runs. In runs 4 and 5, 2 equiv of nitrile was used. [d] Heating times in runs 1, 6, and 7 were 4 h. [e] Heating times in method A. [f] Heating times in method B.

Scheme VI



into *N*-phenyltrichloroborazine[31] (**32**) by heating under dehydrochlorination (see, Scheme VI). Treatment of isolated **32** with **28a** and aluminum trichloride in refluxing dichloroethane or similar treatment in **28a** at 200 °C for 16 h followed by acidic hydrolysis gave recovered aniline **3g** in more than ca. 60% yield besides a small amount of **1a** (6 or 9% respectively). Therefore, a considerable amount of anilines was unavoidably recovered, as the reaction rate of **13b** with **28a** to give **1a** was thought to be comparable to that of **13b** to **32**.

In run 6, the two isomers 4-chloro- (**1g**) and 6-chloro-2-aminobenzophenone (**1h**) were isolated.

Various examples of the similar reaction with secondary anilines **3** and nitriles **28** are shown in Table VIII.

Since secondary anilinodichloroborane (**13a**) has been thought to possess significantly greater thermal stability than primary anilinodichloroborane (**13b**), **13a** was produced previously by heating **3** and boron trichloride at 80 °C for 2 h in the solvents given in Table VIII, followed by treatment with **28** (method A). Coexistence of aluminum trichloride (method B) raised the yield of **1** considerably as can be noted in Table VIII. Further improvement was made in method C. Namely, **13a** was prepared in benzene and the solution was concentrated almost to dryness. To the resulting syrup, 2 equiv of the nitrile was added and the solution was heated at 100 °C for a few hours. Whereas method B in run 8 did not give 5-nitro-2-methylaminobenzophenone (**1r**), method C afforded **1r**, albeit in modest yield. As shown in run 9, the presence of a tertiary amino function did not disturb the reaction when 2 equiv of boron trichloride was used.

To rationalize the pathway of the above reaction, a stabilized cyclic transition state like **33** has to be considered. Namely, the initially formed boron trichloride complex of aniline **17** changes by heating into anilinoborane (**13**). Then **13** reacts with **28** via the cyclic transition state **34,** giving the primary product, iminoboranes **35**. Compound **13** reacts concommitantly with **28** to afford a precursor **36** of *N*-phenylamidine (**30**) as a by-product, especially when **13b** is heated near 150 °C. The coexistence of aluminum trichloride may stabilize **34** by transforming it into tetrachloroaluminate **33,** which would be expected to facilitate the path from **13** to **35** rather than that to **36**. Simultaneously, **13** might react with aluminum trichloride to form a boronium cationic species **37,** which would act as a better Lewis acid than **13** itself in reacting with **28** also to give **33**.

In summary, our process provides a specific ortho hydroxybenzylation and hydroxyalkylation of secondary anilines, the methodology of which has not been known in synthetic organic chemistry. Thus, the compound **6** series [R_1 = (un)-substituted alkyl] can be obtained directly from aniline derivatives under extremely mild conditions. The reaction described above is unique in that no other electrophilic metal halides have exhibited this transformation. Furthermore, the use of anilinodichloroboranes **13** which nitriles allows a one-step synthesis of 2-aminophenyl ketones **1,** which had been accessible only by elaborate routes. Such specific ortho Friedel-Crafts reaction of primary and secondary anilines has not been known in organic synthesis, because ordinary electrophilic metal halides except boron trichloride direct the reaction between anilines and nitriles to produce *N*-phenylamidines **30,** as already described. The uniqueness may stem from the strong Lewis acidity of **13** which allows the existence of a relatively stable transition state such as **33** and **34**. Irrespective of the precise mechanism involved, it is evident that we can now very conveniently carry out a carbon-carbon bond formation of sp^2 or sp and ring carbon atom ortho to the nitrogen function of anilines via **13,** which are readily prepared in situ. Further work is in progress to explore the full synthetic potential of this new reaction.

Experimental Section

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ solution with a Koken DS-207B or JASCO IRS spectrophotometer. Wave numbers are expressed in reciprocal centimeters. NMR spectra were taken in $CDCl_3$ solution on a Varian A-60 or T-60 spectrophotometer. Chemical shifts are expressed as δ values (parts per million) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70–230 mesh ASTM) and aluminum oxide (E. Merck, standarisiert). Silica gel GF (E. Merck) was used for both analytical and preparative thin-layer chromatography (TLC). In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with two to three portions of the indicated solvent and then wash the organic layer with saturated NaCl-H_2O or H_2O and dry it over Na_2SO_4 or $MgSO_4$. The physical properties and analytical data of new products are shown in Table IX and X.

4,4′-Bis(methylamino)triphenylmethane (5b).[17] To a stirred solution of *N*-methylanilinodichloroalane (**10a**)[20] (700 mg, 2.25 mmol) in dry benzene (10 mL) was added a solution of benzaldehyde (**14a**) (239 mg, 2.25 mmol) in dry benzene (2 mL) under ice cooling and N_2 stream. The resulting mixture was allowed to stand for 12 h at room temperature. A portion of the mixture was poured onto ice–2 N Na_2CO_3 and extracted with ether. On TLC, **5b** was found besides *N*-methylaniline (**3a**) and **14a**. The reaction mixture was refluxed for 4 h, turning dark green during this time. After cooling, ice–2 N NaOH was added; then the mixture was extracted with ether. The residue of the extract (540 mg) was purified by TLC (CH_2Cl_2), giving oily **5b** (224 mg, 66% based on **3a**): NMR δ 2.73 (6 H, s, two NCH_3), 3.40 (2 H, s, two NH), 5.38 (1 H, s, CH), 6.5 (d, 4 H, $J_{AX(A'X')}$ = 8 Hz, four ortho aromatic protons to nitrogen), 6.9 (4 H, d, $J_{AX(A'X')}$ = 8 Hz, four meta aromatic protons to nitrogen), 7.21 (5 H, s, Ph).

***N*-Methyl-2-(α-hydroxybenzyl)aniline (6a) (General Procedure in the Absence of Tertiary Amine) (Table I, Run 1).** To a stirred solution of *N*-methylanilinodichloroborane (**13a**)[21] (200 mg, 1.06 mmol) in dry CH_2Cl_2 (7 mL) was added a solution of benzaldehyde (**14a**) (113 mg, 1.06 mmol) in dry CH_2Cl_2 (2 mL) under ice cooling and N_2 stream. After the solution had been stirred for 2 h, it was poured onto ice–2 N HCl and extracted with ether. The organic layer was washed with 2 N HCl and H_2O. Concentration of the organic layer gave recovered **14a** (70 mg, 62%). The acidic layer was alkalized with ice–2 N NaOH and extracted with ether. The residue from the extract was separated by TLC ($CHCl_3$), giving *N*-methylaniline (26 mg, 23%) and **6a** (58 mg, 26%): mp 124–126 °C ($CHCl_3$–petroleum ether), lit.[22] 127–130 °C. An analogous reaction was carried out in refluxing dichloroethane for 2 h, and a curdy precipitate was formed. Workup similar to the above gave a mixture of **5b** and **6a** in a ratio of 1:2 in the basic fraction (comparison of the signals of both benzyl protons at δ 5.38 and 5.78).

***N*-Methyl-2-(α-hydroxy-2-chlorobenzyl)aniline (6b), *N*-Methyl-2-(α-hydroxy-2-nitrobenzyl)aniline (6c), *N*-Methyl-2-(α-hydroxy-4-nitrobenzyl)aniline (6d), *N*-Methyl-2-(α-hydroxy-4-methoxybenzyl)aniline (6e), and *N,O*-4-Dinitrobenzoate of 6e (Table I, Runs 2–5).** In a general procedure analogous to that used for **6a**, *N*-methylanilinodichloroborane (**13a**) (100 mg) was treated with 1 equiv of 2-chlorobenzaldehyde (**14b**), 2-nitrobenzaldehyde (**14c**), 4-nitrobenzaldehyde (**14d**), or 4-methoxybenzaldehyde (**14e**) in CH_2Cl_2. Purification of each basic fraction gave **6b** (43 mg), **6c** (44 mg), **6d** (65 mg), or **6e** (49 mg), respectively.

N,O-4-Dinitrobenzoate of **6e:** a mixed solution of **6e** (99 mg) and 4-nitrobenzoyl chloride (200 mg) in dry pyridine (3 mL) was allowed to stand at room temperature overnight. Ice was added to the solution, which was stirred for 1 h at room temperature. Next, 2 N Na_2CO_3 was added to the mixture, which then was extracted with ether. The organic layer was washed with 2 N HCl and H_2O. Concentration of the organic layer gave the *N,O*-4-dinitrobenzoate of **6e** (143 mg, 65%): mp 190–191 °C (dec) (CH_3OH–CH_2Cl_2); IR 1729 (OC=O), 1643 (NC=O), 1349, and 1527 cm^{-1} (NO_2); NMR δ 2.88 and 3.68 (3 H, two singlets, OCH_3), 3.77 and 3.88 (3 H, two singlets, OCH_3). Anal. Calcd for $C_{29}H_{23}N_3O_8$: C, 64.32; H, 4.27; N, 7.76. Found: C, 64.04; H, 4.39; N, 8.00.

***N*-Methyl-2-(α-hydroxybenzyl)anilines 6a,c–e (General Procedure in the Presence of Tertiary Amine).** To a stirred solution of *N*-methylanilinodichloroborane (**13a**) (100 mg, 0.53 mmol) in dry CH_2Cl_2 (15 mL), a solution of benzaldehyde (**14a**) (57 mg, 0.53 mmol) and tri-*n*-butylamine (**23**) (99 mg, 0.53 mmol) in dry CH_2Cl_2 was added under ice cooling and N_2 stream. After the solution had been stirred for 2 h, it was poured onto ice–2 N HCl and extracted with ether. The ether layer was washed with 2 N HCl and H_2O. The combined acidic layer was alkalized with ice–2 N K_2CO_3 and extracted with CH_2Cl_2. The residue of the extract was purified by TLC ($CHCl_3$), giving **6a** (91 mg, 81%). Analogous treatment of **13a** (100 mg) with 2-nitrobenzaldehyde (**14c**), 4-nitrobenzaldehyde (**14d**), or 4-methoxybenzaldehyde (**14e**) in the presence of **23** gave **6c** (133 mg), **6d** (108 mg) or **6e** (108 mg), respectively.

Influence of Tertiary Amines on the Yield of *N*-Methyl-2-(α-hydroxybenzyl)aniline (6a) (Table II). To a stirred solution of *N*-methylanilinodichloroborane (**13a**) (100 mg) in CH_2Cl_2 or benzene was added a mixed solution of benzaldehyde (**14a**) (62 mg, 1.1 equiv) and tertiary amine (**19, 20, 21, 22, 23, or 24**) (1.1 equiv) in CH_2Cl_2 or benzene under ice cooling and N_2 stream. The clear solution (runs 1, 2, 5–7), the turbid solution (run 4), or the suspension (run 3) were stirred under the above conditions for 0.5 h. After the addition of ice–2 N NaOH, the mixture was extracted with CH_2Cl_2. To remove excess **14a**, which caused formation of 1,3-benzoxazine, the CH_2Cl_2 layer was stirred with 20% $NaHSO_3$–H_2O for 1 h. The organic layer was washed with H_2O, dried, and evaporated. The residue was purified by TLC ($CHCl_3$) and the isolated yield of **6a** was compared as shown in Table II.

Influence of Solvents on the Yield of *N*-Methyl-2-(α-hydroxybenzyl)aniline (6a) (Table III). In a procedure and workup analogous to the above, *N*-methylanilinodichloroborane (**13a**), benzaldehyde (**14a**) (1 equiv), and triethylamine (**21**) (1 equiv) were treated in the solvents indicated in Table III. Stirring was done for 1 instead of 2 h. On addition of **13a** to dimethylformamide (DMF), a thick oil separated immediately. To dissolve this oily precipitate, the experiment was

Table IX. Physical Properties and Analytical Data of Secondary 2-(α-Hydroxybenzyl)anilines (**6**) and Secondary 2-(α-Hydroxyalkyl)-anilines (**26**)

product	mp, °C (from)[a]	IR, cm^{-1}	NMR, δ	anal., found, % (calcd)
6b	111–113 (A)	3585 and 3425[b]	2.83[c] (3 H, s), 3.58[b] (br s), 6.10[d] (1 H, s), 6.6–7.5[e] (8 H, m)	C, 67.60 (67.88) H, 5.71 (5.70) N, 5.65 (5.66) Cl, 14.51 (14.32)
6c	93–95 (A)	3586 and 3436[b]	2.80[c] (3 H, s), 3.72[b] (2 H, s), 6.40[d] (1 H, s), 6.6–8.0[e] (8 H, m)	C, 65.21 (65.10) H, 5.45 (5.46) N, 10.57 (10.85)
6d	127–128 (A)	3604 and 3434[b]	2.71[c] (3 H, s), 3.66[b] (2 H, s), 5.85[d] (1 H, s), 6.5–8.2[e] (8 H, m)	C, 65.10 (65.10) H, 5.52 (5.46) N, 10.78 (10.85)
6e	oil	3588 and 3428[b]	2.70[c] (3 H, s), 3.57[b] (2 H, br s), 3.72[f] (3 H, s), 5.67[d] (1 H, s), 6.5–7.4[e] (8 H, m)	
6f	107–108 (B)	3592 and 3436[b] 1718 (OC=O)	2.75[c] (3 H, s), 3.82[b] (2 H, br s), 3.89 (3 H, s, $COOCH_3$), 5.85[d] (1 H, s), 6.5–8.1[e] (8 H, m)	C, 70.91 (70.83) H, 6.49 (6.32) N, 5.20 (5.16)
6h	106–108 (A)	3586 and 3427[b]	2.84[c] (3 H, s), 3.30[b] (2 H, br s), 6.12[d] (1 H, s), 6.5–7.5[e] (7 H, m)	C, 59.50 (59.58) H, 4.47 (4.65) N, 5.20 (4.97) Cl, 24.83 (25.13)
6i	125–127 (B)	3587 and 3427[b]	2.78[c] (3 H, s), 3.82 (9 H two s), and 3.85,[f] 5.67[d] (1 H, s), 6.5–7.2[e] (5 H, m)	C, 60.37 (60.44) H, 5.98 (5.97) N, 4.10 (4.15) Cl, 10.72 (10.50)
6j	133–135 (B)	3583 and 3410[b]	2.96[c] (3 H, s), 2.96 (1 H, s, and br s), 5.7,[b] 6.1[d] (1 H, s), 6.5–8.2[e] (3 H, ABX pattern, J_{AB} = 9 Hz, J_{BX} = 3 Hz and 4 H, m)	C, 57.72 (57.44) H, 4.60 (4.48) N, 9.50 (9.57) Cl, 12.26 (12.11)
6k	158–161 (B)	3593 and 3430[b]	2.89[c] (3 H, s), 3.78 (9 H, two s), and 3.82,[f] 5.72[d] (1 H, s), 6.5–8.2[e] (5 H, ABX and A_2 pattern, J_{AB} = 9 Hz, J_{BX} = 2 Hz)	C, 58.44 (58.61) H, 5.82 (5.79) N, 8.08 (8.04)
6l	oil	3593 and 3358[b]	0.93 (6 H, t, J = 7 Hz, two CH_3CH_2N), 2.45 (4 H, q, J = 7 Hz, two CH_3CH_2N), 2.5 and 3.1 (4 H, A_2B_2 pattern, NCH_2CH_2N), 3.7 and 4.0[b] (2 H, br s), 6.02[d] (1 H, s), 6.5–7.5[e] (7 H, m)	
6m	132–135 (B)	3417 and 3357[b] 1666 (OC=O) (Nujol)	1.32 (3 H, t, J = 7 Hz, CH_3CH_2O), 2.75[c] (3 H, s), 4.25 (2 H, q, J = 7 Hz, OCH_2CH_3), 5.75[d] (1 H, s), 6.6–7.9[e] (3 H, ABX pattern, J_{AB} = 8 Hz, J_{BX} = 2 Hz and 5 H, s)	C, 71.45 (71.56) H, 6.87 (6.71) N, 4.97 (4.91)

Table IX (*Continued*)

product	mp, °C (from)[a]	IR, cm^{-1}	NMR, δ	anal., found, % (calcd)
6n	106–107 (B)	3602 and 3430[b]	2.63[c] (3 H, s), 3.8[b] (2 H, br s), 6.62[d] (1 H, s), 6.4–7.4[e] (3 H, ABX pattern, $J_{AB} = J_{BX} =$ 8 Hz, $J_{AB} = 1.5$ Hz and 5 H, s)	C, 67.81 (67.88) H, 5.84 (5.70) N, 5.69 (5.65) Cl, 14.37 (14.31)
6o	88–89 (B)	3590 and 3430[b]	2.71[c] (3 H, s), 3.5[b] (2 H, br s), 5.76[d] (1 H, s), 6.5–7.3[e] (3 H, m and 5 H, s)	C, 67.84 (67.88) H, 5.80 (5.70) N, 5.72 (5.65) Cl, 14.26 (14.31)
26a	oil	3595 and 3425[b]	0.92 (3 H, t, $J = 7$ Hz CH_3CH_2), 1.15–2.1 (4 H, m $CH_3CH_2CH_2CH$), 3.28[b] (2 H, br s), 4.68[d] (1 H, t, $J = 7$ Hz), 6.5–7.4[e] (4 H, m)	
26b	75–78 (B)	3595 and 3425[b]	1.63 (6 H, s two CH_3), 2.84[c] (3 H, s), 3.64[b] (2 H, br s), 6.5–7.2[e] (4 H, m)	C, 72.59 (72.69) H, 9.24 (9.15) N, 8.20 (8.48)

[a] A, chloroform–petroleum ether. B, ether–petroleum ether. [b] NH and OH. [c] NCH_3. [d] Benzyl proton. [e] Aromatic protons. [f] OCH_3.

carried out in a mixed solvent of DMF and CH_2Cl_2 in the ratio of 4:3. Purification of the basic fraction by TLC ($CHCl_3$) and the isolated yield of **6a** was compared as shown in Table III.

Preparation of *N*-Methyl-2-(α-hydroxybenzyl)aniline (6a) by "One-Pot Reaction" (General Procedure) (Table IV, Run 1). To a stirred solution of boron trichloride (29.7 g, 0.25 mol) in dry benzene (300 mL) was added a solution of *N*-methylaniline (**3a**) (25.0 g, 0.23 mol) in dry benzene (100 mL) under ice cooling and N_2 stream. The solution was refluxed for 2 h, while the hydrogen chloride being liberated was collected in a dilute NaOH solution. After the solution had been cooled and the remaining hydrogen chloride had been expelled with N_2 stream, a mixed solution of benzaldehyde (**14a**) (27.2 g, 0.25 mol) and triethylamine (65.0 mL, 0.46 mol) in dry benzene (150 mL) was added dropwise to the above solution under ice cooling over a period of 15 min. TLC of a portion which was worked up immediately after the addition showed completion of the reaction. The yellow turbid solution was stirred for 1 h at room temperature. Ice–2 N HCl was added, and the mixture was extracted with ether. The ether phase was washed with 2 N HCl and H_2O. The combined acidic layer was alkalized with ice–K_2CO_3, and the mixture was extracted with ether. Concentration of the organic layer and recrystallization gave **6a** (40.5 g). The second crop (1.40 g, mp 112–115 °C) was treated with Norit in MeOH and recrystallized from ether–petroleum ether, giving additional **6a** (1.31 g); total yield of **6a** was 84%.

***N*-Methyl-2-(α-hydroxy-4-methoxycarbonylbenzyl)aniline (6f), 4-Chloro-*N*-methyl-2-(α-hydroxybenzyl)aniline (6g), 4-Chloro-*N*-methyl-2-(α-hydroxy-2-chlorobenzyl)aniline (6h), and 4-Chloro-*N*-methyl-2-(α-hydroxy-3,4,5-trimethoxybenzyl)aniline (6i).** In a procedure and workup analogous to the above, *N*-methylaniline (**3a**) or 4-chloro-*N*-methylaniline (**3b**) was treated with boron trichloride (1.1 equiv) followed by a mixed solution of benzaldehyde (**14h, a, b,** or **g**) (1.1 equiv) and triethylamine (1.1 to 2 equiv) in corresponding solvents. Direct crystallization of the residue of the basic fraction (run 2) or purification by TLC [CH_2Cl_2 in runs 3 and 4, $CHCl_3$–EtOAc (2:1) in run 5] gave **6f–i**, respectively.

4-Nitro-*N*-methyl-2-(α-hydroxy-2-chlorobenzyl)aniline (6j) and 4-Nitro-*N*-methyl-2-(α-hydroxy-3,4,5-trimethoxybenzyl) aniline (6k). In a manner analogous to the above, 4-nitro-*N*-methylaniline[36] (**3c**) was treated with boron trichloride (1.1 equiv) in dichloroethane and then with a mixed solution of benzaldehyde **14b** or **g** (1.1 equiv) and triethylamine (1.1 to 2 equiv) in dichloroethane. Ice–2 N K_2CO_3 was added to the solution and the mixture was extracted with CH_2Cl_2. Concentration of the organic layer (run 7) followed by chromatographic purification (run 6) gave **6j** or **6k**, respectively. **6j:** Chromatography (silica gel) of the residue gave recovered **14b** (ca. 10%) from the benzene eluate and **6j** from the CH_2Cl_2 eluate. **6k:** The concentrated residue of the mother liquor of the first corps was chromatographed (silica gel). The eluate with $CHCl_3$ was concentrated to give recovered **3c** (15%). The eluate with $CHCl_3$ containing 2% MeOH was concentrated to give additional **6k.** Total yield was 71%.

4-Chloro-*N*-diethylaminoethyl-2-(α-hydroxy-2-fluorobenzyl)aniline (61). In a procedure and workup analogous to the above, 4-chloro-*N*-diethylaminoethylaniline[37a] (prepared according to lit.[37b]) (**3d**) was treated with boron trichloride (2 equiv) followed by a mixed solution of benzaldehyde (**14i**) (1 equiv) and triethylamine (1.2 equiv) in dichloroethane. Chromatography of the basic extract (Al_2O_3, elution with $CHCl_3$) gave oily **61** (81%).

4-Ethoxycarbonyl-*N*-methyl-2-(α-hydroxybenzyl)aniline (6m). To a stirred solution of 4-ethoxycarbonyl-*N*-methylaniline (**3e**) (179 mg, 1 mmol) in dry benzene (2 mL) was added a solution of boron trichloride (129 mg, 1.1 mmol) in dry benzene (2 mL) under ice cooling and N_2 stream. To this solution, a mixed solution of benzaldehyde (**14a**) (0.1 mL, 1 mmol) and triethylamine (0.31 mL, 2.2 mmol) was added dropwise under the above conditions. The resulting mixture was stirred for 3 h at room temperature. Ice was added and the mixture was extracted with ether. The organic layer was stirred with a 10% $NaHSO_3$ solution (10 mL) for 0.5 h. The organic layer was washed with H_2O, dried, concentrated, and recrystallized to obtain **6m** (196 mg, 69%).

3-Chloro-*N*-methyl-2-(α-hydroxybenzyl)aniline (6n) and 5-Chloro-*N*-Methyl-2-(α-hydroxybenzyl)aniline (6o). In a procedure and workup analogous to those for **6a**, a solution of 3-chloro-*N*-methylaniline (**3f**) (525 mg) in dichloroethane (5 mL) was treated with boron trichloride (389 mg, 1.1 equiv) and then with a mixed solution of benzaldehyde (14a) (0.31 mL, 1 equiv) and triethylamine (0.92 mL 2.2 equiv) in dichloroethane. Repeated (three times) recrystallization of the concentrated residue of the basic extract gave **6n** (266 mg). The combined mother liquor was concentrated and purified by TLC (benzene). Elution of the less polar fraction and recrystallization of the concentrated eluate gave additional **6n** (217 mg). Total yield of **6n**, 65%. Elution of the more polar fraction and recrystallization of the concentrated eluate gave **6o** (141 mg, 19%).

***N*-Methyl-2-(1-hydroxybutyl)aniline (26a), *N,O*-4-Dinitrobenzoate of 26a, and *N*-Methyl-2-(1-hydroxy-1-methylethyl)aniline (26b) (Table V).** In a procedure analogous to that for **6a**, *N*-methylanilinodichloroborane (**13a**) (153 mg) was treated with *n*-propylaldehyde (1 equiv)

Table X. Physical Properties and Analytical Data of Primary and Secondary 2-Aminophenyl Ketones (**1**)

product	mp, °C (from)[a]	IR, cm^{-1}	NMR, δ	anal. found, % (calcd)
1b[28a]	oil	3457, and 3350,[b] 1640, 1618, 1585	2.55 (3 H, s, CH_3), 6.4-7.6[d] (4 H, m)	
1f[15]	oil	3500, and 3350,[b] 1635, 1610, 1574	6.52[e] (1 H, d of d, J_{AX} = 8 Hz, J_{BX} = 7 Hz), 7.2-7.7[d] (7 H, m)	
1i[15]	oil[g]	3505, and 3380,[b] 1633, 1580	3.63 (3 H, s, OCH_3), 5.70[b] (2 H, br s), 7.7-6.6[d] (8 H, m)	
1j-acetate	63-64 (A)	3242,[c] 1700, 1656, 1600, 1573	2.20 (2 H, quint, J = 7 Hz, CH_2), 2.22 (3 H, s, NAc), 3.20 (2 H, t, J = 7 Hz, CH_2), 3.67 (2 H, t, J = 7 Hz, CH_2), 7.05[i] (1 H, d of d, J_{AB} = 8 Hz, J_{BX} = 2 Hz), 7.85[h] (1 H, d, J_{AB} = 8 Hz), 8.82[f] (1 H, d, J_{BX} = 2 Hz)	C, 52.51 (52.51) H, 4.76 (4.78) N, 5.18 (5.16) Cl, 25.71 (25.87)
1l	67-68 (B)	3230,[c] 1622, 1590, 1570	2.95[j] (3 H, d, J = 5 Hz), 6.4-7.5[d] (8 H, m), ~8.8[c] (1 H, br s)	C, 68.52 (68.43) H, 4.95 (4.93) N, 5.64 (5.70) Cl, 14.41 (14.43)
1m	117-119 (C)	3320,[c] 1621, 1572	2.96[j] (3 H, d, J = 5 Hz), 6.4-8.4[d] (9 H, m)	C, 65.55 (65.62) H, 4.81 (4.72) N, 11.12 (10.93)
1n	39-40 (B)	3334,[c] 1636, 1571	1.20[k] (3 H, d, J = 7 Hz), 2.88[j] (3 H, d, J = 5 Hz), 2.97[l] (2 H, q, J = 7 Hz), 6.4-7.9[d] (4 H, m), ~8.7[c] (1 H, br s)	C, 73.81 (73.59) H, 7.96 (8.03) N, 8.86 (8.58)
1o	bp_3 122-123	3317,[c] 1639, 1573	0.92[k] (3 H, t, J = 6 Hz), 1.1-1.9 (4 H, m, $CH_3CH_2CH_2CH_2$-), 2.88 (2 H, q, J = 6 Hz, O=CCH_2CH_2-), 2.98[j] (3 H, d, J = 5 Hz), 6.4-7.9[d] (4 H, m), ~8.7[c] (1 H, br s)	C, 75.80 (75.35) H, 8.98 (8.96) N, 7.36 (7.32)

[a] A, CH_2Cl_2-*n*-hexane; B, *n*-hexane; C, MeOH. [b] NH_2. [c] NH. [d] Aromatic protons. [e] C_5 proton of the aniline ring. [f] C_3 proton of the aniline ring. [g] Lit.[15] mp 51-52 °C. [h] C_6 proton of the aniline ring. [i] C_4 proton of the aniline ring. [j] NCH_3. [k] CH_3CH_2-. [l] CH_3CH_2-.

and tri-*n*-butylamine (**23**) (1 equiv) in CH_2Cl_2. Ice-2 N K_2CO_3 was added and the mixture was extracted with CH_2Cl_2. Purification of the residue from the CH_2Cl_2 extract by TLC (CH_2Cl_2) gave **26a** (oil, 56 mg, 38%). **26a** (56 mg) was treated with 4-nitrobenzoyl chloride in a mixed solution of pyridine and CH_2Cl_2 as in the experiment for *N,O*-4-dinitrobenzoate of **6e**, giving the corresponding 4-dinitrobenzoate. The residue of the extract was purified by TLC (CH_2Cl_2), giving *N,O*-4-dinitrobenzoate (80 mg) and *N*-4-nitrobenzoate (62 mg). Recrystallization of the former fraction gave the *N,O*-4-dinitrobenzoate of **26a** (52 mg): mp 131-133 °C (MeOH); IR 1725 (OC=O), 1643 (NC=O), 1527, and 1350 cm^{-1} (NO_2); NMR δ 0.97 (3 H, t, J = 7 Hz, -CH_2CH_3), 1.15-2.25 (4 H, m, -$HCCH_2CH_2CH_3$), 3.50 and 3.62 (3 H, two singlets, NCH_3), 5.84-6.34 (1 H, m, methine proton). Anal. ($C_{25}H_{23}N_3O_7$) C, H, N. *N*-4-Nitrobenzoate of **26a** (oil): IR 3600 (OH), 1638 (N-C=O). In a procedure analogous to that in the above experiment, **13a** (100 mg) was treated with acetone and **23** in CH_2Cl_2. Purification of the residue of the extract by TLC (CH_2Cl_2) gave **26b** (7 mg, 8%).

2-Aminobenzophenone (1a) and *N*-Phenylbenzamidine (30a). (a) Runs 1 and 2 in Table VI. To a stirred solution of boron trichloride (645 mg, 5.5 mmol) in benzene or tetrachloroethane (ca. 3 mL) was added a solution of aniline (466 mg, 5 mmol) in corresponding solvent (5 mL) under ice cooling. To the resulting aniline-boron trichloride complex, benzonitrile (**28a**) (0.6 mL, 6 mmol) was added and the mixture was refluxed for 6 h, during which time the complex dissolved. After cooling, 2 N HCl (10 mL) was added and the mixture was warmed under stirring at 80 °C for 20 min to hydrolyze the corresponding ketimine. The mixture was extracted with CH_2Cl_2 to separate the neutral fraction containing **1a** and the recovered **28a**. To separate **1a** from **28a**, a mixed solution of 95% EtOH (5 mL) and 2 N NaOH (10 mL) was added to the neutral fraction, and the mixture was refluxed for 1 h under stirring to hydrolyze the recovered **28a**. After cooling,

H_2O was added and the mixture was extracted with CH_2Cl_2. After washing with H_2O, drying, and removal of CH_2Cl_2, the resulting residue was dissolved in benzene and filtered on a silica gel layer (5 g) to remove benzamide. The concentrated eluate was purified by TLC (CH_2Cl_2), giving **1a:** mp 107–108 °C (CH_2Cl_2–hexane), lit.[13] mp 107–108 °C, and a small amount of unidentified substance (2 and 11 mg, no carbonyl absorption in the IR spectra). The combined acidic layer was alkalized with 2 N NaOH and extracted with CH_2Cl_2. The extract contained aniline (60–70%) and *N*-phenylbenzamidine (**30a**). After removal of aniline under reduced pressure, **30a** was obtained: mp 116–117 °C (CH_2Cl_2–hexane), lit.[25] mp 116 °C.

(b) Runs 3 to 10 in Table VI. To a stirred solution of boron trichloride (645 mg, 5.5 mmol) in the solvent (ca. 3 mL) indicated for each run was added a solution of aniline (466 mg, 5 mmol) in the same solvent (5 mL) under ice cooling. To the mixture, the benzonitrile (1.1 to 2 equiv, see footnote in Table VI) and the Lewis acid (5.5 mmol) indicated in each run were added. In run 3, the precipitate dissolved immediately after refluxing. In runs 4 to 7, the precipitate dissolved within 10 min at room temperature and the solution was refluxed for 3 to 6 h (see footnote in Table VI). In runs 8 to 10, the precipitate did not dissolve during refluxing. The workup was similar to that described in a. In runs 8 and 10, the acidic layer was made alkaline with 2 N NaOH or concentrated NH_4OH, and the precipitate was filtered on a Celite layer. The layer was washed with CH_2Cl_2. The filtrate was extracted with the dichloromethane. In run 9, the acidic layer was made alkaline with concentrated NH_4OH and extracted with CH_2Cl_2.

General Procedure for the Table VII Experiment. To a stirred solution of boron trichloride (1 to 1.1 equiv based on an aniline) in the solvent indicated for each run was added dropwise a corresponding solution of an aniline under ice cooling. To the resulting boron trichloride–aniline derivative complex, a nitrile (1.1 to 2 equiv, see footnote *b* in Table VII) and aluminum trichloride (1.1 equiv) were added successively. Within 10 to 20 min, the complex and aluminum trichloride dissolved during stirring at room temperature. The solution was then refluxed for the time indicated in Table VII, while the solution separated into two layers. After cooling, ice–2 N HCl was added under stirring and then the mixture was warmed at 80 °C for 30 min to hydrolyze the ketimine. The mixture was extracted with CH_2Cl_2 to separate the 2-aminophenyl ketone and the recovered nitrile as the neutral fraction. The acidic layer was made alkaline with 2 N NaOH and extracted with CH_2Cl_2 to separate the recovered aniline derivative and *N*-phenylbenzamidine as the basic fraction.

2-Aminoacetophenone (1b). In run 1, both the neutral and basic fractions contained 1-aminoacetophenone in a ratio of about 1:5. Both fractions were combined, dissolved in benzene, and washed with 5% AcOH and H_2O. The benzene layer was washed with aqueous $NaHCO_3$ and H_2O. The extract was dissolved in CH_2Cl_2 and filtered in a silica gel layer to remove a polar fraction. The concentrated eluate contained **1b** [oil, one spot on TLC (CH_2Cl_2)]. *N*-Acetate of **1b:** mp 74–76 °C (ether–*n*-hexane), lit.[28b] mp 76–77 °C.

2-Aminophenyl Benzyl Ketone (1c). In run 2, the neutral fraction was heated at 100 °C for 1 h with 60% H_2SO_4 (wt %) to hydrolyze excess benzylnitrile. After being cooled, the mixture was extracted with CH_2Cl_2. The organic layer was washed with 1 N $NaHCO_3$ and H_2O. The extract was dissolved in benzene and filtered on an Al_2O_3 layer to remove a polar fraction. The eluate was recrystallized to give **1c:** mp 102–103 °C (CH_2Cl_2–*n*-hexane), lit.[14b] mp 103–104 °C.

2-Amino-α-chloroacetophenone (1d), 5-Chloro-2-aminobenzophenone (1e), 3-Chloro-2-aminobenzophenone (1f), 4-Chloro-2-aminobenzophenone (1g), 6-Chloro-2-aminobenzophenone (1h), and 5-Methoxy-2-aminobenzophenone (1i). In run 3, the neutral fraction showed only one spot on TLC (CH_2Cl_2). **1d:** mp 112–113 °C (CH_2Cl_2–*n*-hexane), lit.[29] mp 112–113 °C. In runs 4 to 7, the neutral fraction was treated with a solution of 95% EtOH and 2 N NaOH to separate **1** from **28** as described for **1a. 1e:** mp 97–98 °C (CH_2Cl_2–*n*-hexane), lit.[30] 99 °C. In run 6, the concentrated residue of the mother liquor of **1g** was purified on TLC (topless method, benzene), giving **1h. 1g:** mp 82–83 °C (*n*-hexane), lit.[15] mp 84–85 °C. **1h:** mp 99–100 °C (*n*-hexane), lit.[15] mp 101–102 °C. For physical data of **1f** and **1i**, see Table X.

4-Chloro-2-amino-γ-chlorobutyrophenone (1j) and Its *N*-Acetate. In run 8, the neutral fraction (ca. 20 g of curde **1j**) extracted with benzene was warmed with acetic anhydride (60 mL) at 80 °C for 30 min. After removal of excess acetic anhydride under reduced pressure, the residue was dissolved in benzene and chromatographed through a column containing silica gel (60 g). The combined eluate with CH_2Cl_2 was concentrated and recrystallized, giving the *N*-acetate of **1j.**

General Procedure for the Table VIII Experiment. Method A. To a stirred solution of boron tricholoride (1.1 equiv based on a secondary aniline) in tetrachloroethane was added a solution of a secondary aniline in the same solvent under ice cooling, and the solution was warmed at for 80 °C under nitrogen. After cooling, a nitrile was added to the solution which was refluxed for the time indicated in Table VIII. Workup was as described for **1a.**

2-Methylaminobenzophenone (1k). To separate **1k** from **28a,** the neutral fraction was treated with a mixed solution of 95% EtOH and 2 N NaOH followed by extraction and filtration on a silica gel layer as described for **1a.** Recrystallization of the concentrated eluate gave **1k:** mp 66–68 °C ($CHCl_3$–petroleum ether), lit.[33] mp 69 °C. From the basic fraction, **3a** (45%) was recovered.

2-Methylamino-2′-chlorobenzophenone (1l). The separation of **1l** from recovered 2-chlorobenzonitrile (**28e**) was analogous to the method used to separate **1k.** The recovered crude **3a** amounted to 40%.

2-Methylamino-3′-nitrobenzophenone (1m). The neutral fraction was dissolved in $CHCl_3$ and passed through a silica gel layer. The concentrated eluate was recrystallized to give pure **1m.** The mother liquor was concentrated and purified on TLC (*n*-hexane–ether, 3:1) giving additional pure **1m.** The recovered crude **3a** amounted to 40%.

2-Methylamino-*n*-valerophenone (1o). The neutral fraction was purified on TLC (benzene) giving oily **1o.**

5-Chloro-2-methylaminobenzophenone (1p). The neutral fraction was purified on a silica gel column. Elution with benzene and recrystallization of the concentrated eluate gave **1p:** mp 93–94 °C ($CHCl_3$–petroleum ether), lit.[15] mp 94–95 °C. The recovered crude **3b** amounted to ca. 70%.

5-Chloro-2-methylamino-2′-chlorobenzophenone (1q). The separation of **1q** from recovered **28e** was analogous to the method used to separate **1k**:**1q:** mp 87–89 °C (ether–*n*-hexane), lit.[15] mp 88–90 °C.

Method B. The procedure was essentially the same as that used for method A. Changes involved the addition of a nitrile followed by 1.1 equiv of aluminum trichloride based on the aniline. For the amounts of nitrile and solvent used in each run, see footnote *c* in Table VIII. During refluxing, the solution separated into two layers. Workup was as described for **1a.**

2-Methylaminopropiophenone (1n). The neutral fraction was purified on a silica gel layer. Elution with benzene and recrystallization of the concentrated eluate gave **1n.**

5-Chloro-2-(diethylaminoethyl)aminobenzophenone (1s). 4-Chloro-*N*-diethylaminoethylaniline[37a] (**3d**) (prepared according to lit.[37b]) was treated with boron trichloride (2.1 equiv based on **3d**), benzonitrile (1.1 equiv), and aluminum trichloride (1.1 equiv) in tetrachloroethane (6 mL) according to the general procedure in method B. After being treated with 2 N HCl for 30 min at 80 °C, the mixture was extracted with ether. The combined acidic layer was made alkaline with 2 N NaOH and extracted with ether. The extract was dissolved in $CHCl_3$ and passed through a silica gel layer (8 g). The eluate with $CHCl_3$ was concentrated, giving oily **1s** [570 mg, one spot on TLC ($CHCl_3$ containing 20% CH_3OH)]. **1s** HCl: mp 192–193 °C (2-propanol), lit.[35] mp 197–199 °C.

Method C. To a stirred solution of boron trichloride (1.1 equiv based on a secondary aniline) in benzene was added a solution of a secondary aniline in benzene under ice cooling. The solution was warmed at 80 °C for 2 h under nitrogen and then concentrated almost to dryness. To the resulting syrup, an excess of a nitrile (3 equiv) was added and the mixture was heated at 100 °C for several hours (heating time, see footnote *d* in Table VIII). Workup was as described for **1a.**

5-Nitro-2-methylaminobenzophenone (1r). Chromatographic purification with silica gel (elution with $CHCl_3$) coupled with TLC ($CHCl_3$) gave **1r,** mp 164–166 °C (CH_2Cl_2–CH_3OH), lit.[34] 159–161 °C, and recovered **28a** (10%).

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Synthesis of Acetylenes from Carboxylic Acid Derivatives via β-Keto Sulfones

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Abstract: Mono- and disubstituted acetylenes **5** are synthesized from carboxylic acid derivatives via the readily accessible β-keto sulfones **3**. Reaction of esters, acid chlorides, and nitriles with lithiated derivatives of alkyl aryl sulfones affords the β-keto sulfones **3**, which are converted to the enol phosphates **4** via the sodium or potassium enolates (Y = OEt, NMe_2) or with catalysis by 4-dimethylaminopyridine (Y = OPh). Reductive elimination of the enol phosphates **4** with sodium in liquid ammonia or sodium amalgam in tetrahydrofuran leads to the alkynes **5**. This use of β-keto sulfones is also applied to the synthesis of cyclododecyne from cyclododecanone.

The carbonyl to olefin transformation is one of the most ubiquitous and useful carbon–carbon bond-forming methods in organic synthesis. Few direct means exist, however, for the analogous transformation of a carboxyl derivative to an acetylene. Moreover, the structural and regiochemical limitations of the common acetylene syntheses[2] via alkylation or dehydrohalogenation make a general procedure for the carboxyl to alkyne conversion highly desirable. Condensation of a carboxyl derivative with a phosphorus ylide, followed by pyrolysis of the resultant α-keto phosphorane, provides a solution to this problem.[3] However, this sequence has been restricted to the preparation of disubstituted alkynes conjugated to ester, nitrile, or aryl groups, and the pyrolysis conditions preclude its application to sensitive or highly functionalized molecules.

The introduction of a π bond by reductive elimination is central to a variety of alkene syntheses,[4] but its utility in the formation of alkynes has been limited because the appropriate precursors (e.g., 1,2-dihaloethylenes) have generally been prepared from the alkynes themselves. The deoxygenation of benzil by reduction of a 1,3,2-dioxaphosphole with magnesium is one exception.[2k] Because the arylsulfonyl group facilitates carbanion and therefore carbon–carbon bond formation, and both the arylsulfonyl[4g,5] and phosphate[4i,6] moieties undergo reductive removal, we chose to investigate the reaction sequence of Scheme I as a new alkyne synthesis. The successful outcome of this study and the preparation of a variety of acetylenes is presented in Table I and discussed below. α-Sulfonyl ketones **3** are also available from enolate sulfenylation[7] or sulfinylation[8] and subsequent oxidation, so this procedure is useful for the conversion of ketones to alkynes as well.

Synthesis of β-Keto Sulfones. β-Keto sulfones can be prepared in good yield by the acylation of sulfonyl carbanions with carboxylic acid chlorides and esters.[9] The initial product of the

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