Direct Substitution of Aromatic Ethers by Lithium Amides. A New Aromatic Amination Reaction

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Reaction of lithiated dialkylamines with methoxy aromatics in refluxing THF leads to products resulting from a direct ipso-substitution. Especially with lithiated secondary amines high conversions and selectivities are achieved. Sulfonyl-substituted aromatics react equally well, but halogenated aromatics give rise to side-products arising from a competing pathway via aryne intermediates. The scope and mechanistic implications of this novel nucleophilic amination reaction are described.

The introduction of an amino function into aromatic compounds by way of nucleophilic substitution is usually carried out with halogenated aromatics.[1] Such substitutions are regioselective only in the special case that an electron-withdrawing group is present in the ortho or para position. The regioselectivity is lost when a benzyne intermediate is involved. Such is the case in many of the substitutions of halogenated aromatics.[1]

In a few scattered reports the nucleophilic substitution of unactivated methoxy aromatics has been reported. Benkeser and DeBoer reported in 1956 that treatment of anisole with lithium dimethylamide resulted in the formation of *N,N*-dimethylaniline in very low yield.[2] The use of sodium amide in boiling piperidine for the dealkylation of aromatic ethers was advocated by Brotherton and Bunnett in 1957. *N*-Phenylpiperidine was isolated in very low yield (along with a high yield of phenol) from the reaction with *n*-butoxybenzene.[3] In 1973 Cuvigny and Normant described the reaction of lithium amides with aromatic ethers in HMPA. In addition to dealkylation, resulting in phenols, dealkoxylation, providing aromatic amines, also occurred.[4] Acceptable yields were obtained only with lithium dimethylamide. Finally, in 1977 Meyers and Gabel showed that methoxy aromatics having an *o*-oxazolinyl moiety, when treated with lithium amides, underwent substitution of the methoxy group, thus affording aromatic amines having an *o*-oxazolinyl moiety.[5] This latter reaction may, however, be considered an example of an activated methoxy aromatic, due to the presence of the electron-withdrawing oxazolinyl moiety (when a second methoxy group is present in the meta position only the *o*-methoxy group is substituted). Recently, in two papers the regioselective substitution of a methoxy group for an alkyl group in very specific aromatic ethers by reaction of the methoxy compound with alkyllithiums has been described.[6,7]

We have now discovered that lithium amides in THF can efficiently substitute methoxy groups in unactivated methoxy aromatics[8] in a completely regioselective fashion and in a good yield. Hence, the substitution of methoxy groups by amines is neither limited to methoxy aromatics having activating groups[1] or an *o*-oxazolinyl group,[5] nor does it have to be performed in the carcinogenic HMPA.[4] As an example, heating a mixture of veratrole and 1.25 equiv of *N*-lithio-*N'*-methylpiperazine in THF for 5 h furnishes an 85% yield of the direct substitution product **2** as the only positional isomer. Some starting material is also present as well as a small amount of dealkylation product (Scheme I).

Since we expect this direct substitution to become of major importance in organic synthesis, we have made an investigation of the scope of this transformation.[9] Because of the pharmaceutical importance of arylpiperazines, we have looked especially at this class of compounds which hitherto has usually been prepared from an aniline and the highly toxic *N,N*-bis(2-chloroethyl)amines.[9]

Aromatic Ethers. A number of aromatic ethers has been subjected to our amination conditions. The results of the reaction with 1.1 equiv of *N*-lithio-*N'*-methylpiperazine under reflux in THF (generally overnight) are shown in Table I. From this table it can be concluded that our amination reaction is applicable to a wide range of aromatic ethers and that the amination reaction is completely regioselective. In the case of dialkoxy or trialkoxy compounds small amounts of disubstitution product can usually be detected by GC. Other common side-products in the amination reaction are the corresponding phenol, resulting from dealkylation under the reaction conditions, and varying amounts of starting materials. This dealkylation is more prominent in the case of ethoxybenzene (entry 7; although with lithium piperidide a 35% yield of substitution product was obtained), a feature already cited by Cuvigny and Normant.[4]

With 1,2,3-trimethoxybenzene (entry 4; the same holds for 1,2,3-tris(benzyloxy)benzene) it appears that only the outermost methoxy group is substituted. This observation is in contrast to the reactions with the oxazolines of Meyers, where only the inner methoxy group is substituted in 2,3-dimethoxy-1-oxazolinylbenzene.[5] This supports our as-

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(1) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; Chapter 13 and refs cited therein.

(2) Benkeser, R. A.; DeBoer, C. E. *J. Org. Chem.* **1956**, *21*, 365.

(3) Brotherton, T. K.; Bunnett, J. F. *Chem. Ind. (London)* **1957**, 80.

(4) Cuvigny, Th.; Normant, H. *J. Organomet. Chem.* **1973**, *55*, 41.

(5) Meyers, A. I.; Gabel, R. *J. Org. Chem.* **1977**, *42*, 2653.

(6) Budzelaar, P. H. M.; van Doorn, J. A. *Rec. Trav. Chim. Pays-Bas* **1990**, *109*, 443.

(7) Matsumoto, T.; Kakigi, H.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 4337.

(8) In an attempt to cause lithiated veratrole to react with methoxyamine, the methoxyamine was generated from its hydrochloride with KOH in DMF. The gaseous products (apparently containing some dimethylamine) were led through the solution of the lithioveratrole; from the reaction mixture we isolated 2-methoxy-*N,N*-dimethylaniline.

(9) Eur. Pat. 92200468 (to Solvay-Duphar, Weesp, The Netherlands).

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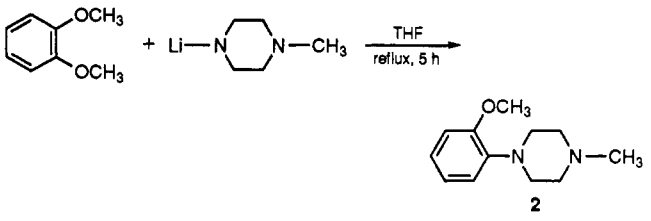
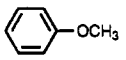
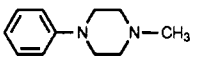
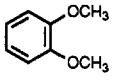
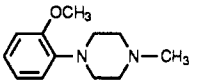
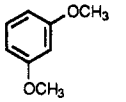
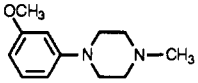
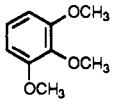
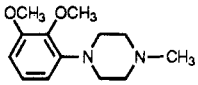
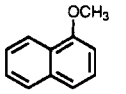
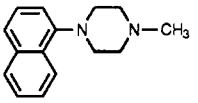
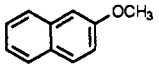
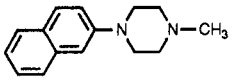
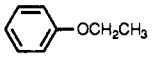
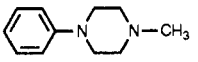
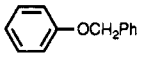
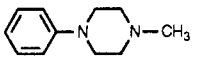
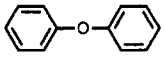
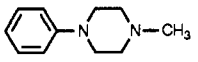
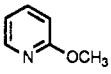
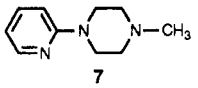
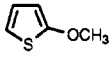
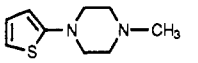
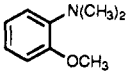
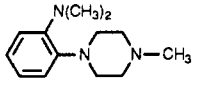
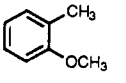
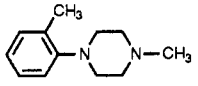
Scheme I



2

Table I. Reaction of Aromatic Ethers with 1.1 Equiv of *N*-Lithio-*N'*-methylpiperazine

entry	aromatic ether	product	yield (%)
1		 1	44
2		 2	75
3		 3	73
4		 4	65
5		 5	69
6		 6	68
7		 1	20
8		 1	63
9		 1	70
10		 7	86
11		 8	22
12		 9	50
13			0

sumption that a mechanism different from the one in our amination reaction is operative in the oxazoline case. Proof of the fact that only the outermost methoxy group is substituted in 1,2,3-trimethoxybenzene was provided by the conversion of 2,3-dimethoxybenzoic acid and 2,6-dimethoxybenzoic acid, respectively, into the known 2,3-dimethoxyaniline and 2,6-dimethoxyaniline, respectively, through a Curtius reaction.[10,11] These anilines were then transformed in a standard fashion to the corresponding piperazines using *N,N*-bis-(2-chloroethyl)methylamine. The piperazine obtained from 2,3-dimethoxybenzoic acid proved to be identical to the piperazine obtained from the reaction of 1,2,3-trimethoxybenzene with *N*-lithio-*N'*-methylpiperazine.

It can also be seen from the Table I that our amination reaction is not limited to methoxy aromatics but that some other aromatic ethers, namely phenyl ethers and benzyl ethers, also undergo the substitution reaction (entries 8 and 9). The fact that (benzyloxy)benzene is a very good substrate is particularly surprising because this is in contrast to the reaction of lithium dimethylamide with (benzyloxy)benzene in HMPA where a Wittig rearrangement takes place resulting in diphenylmethanol.[4]

Amines. Veratrole has been subjected to the action of a variety of lithium amides (1.1 equiv of amide in THF under reflux). The results are shown in Table II. In general, secondary amines give a good yield of the substitution product, the exception being the less-nucleophilic lithium amide from *N*-methylaniline (entry 16). Primary amines are less suitable candidates for the amination reaction; for instance butylamine gives a 28% yield of the *N*-butylaniline **22** (entry 18). In this case there is also present a small amount of N-methylated **22** as judged from the NMR spectrum of the product. Apparently, *N*-butyl-*N*-lithioamine gives some demethylation, the resulting *N*-butylmethylamine then undergoes lithiation and substitutes the methoxy group (some N-methylated material was also observed in the piperazine case (entry 4) and the homopiperazine case (entry 10)).

Hindered secondary amines such as lithium diisopropylamide and lithium tetramethylpiperidide (entries 7 and 14) are also unreactive under the standard conditions. Actually, the common use of lithium diisopropylamide in deprotonation reactions may have prevented a prior discovery of the nucleophilic amination of alkoxy aromatics. This hindrance is used to advantage in the preparation of the piperazines **14** and **15** (entries 5 and 6), which are otherwise difficultly accessible.

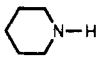
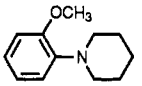
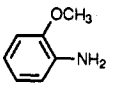
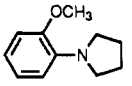
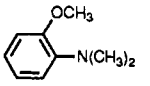
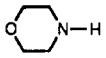
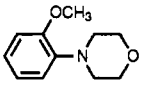
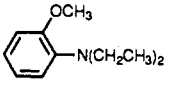
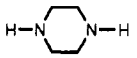
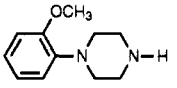
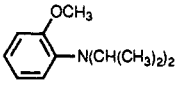
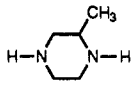
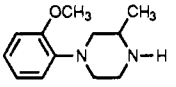
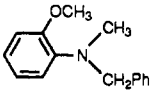
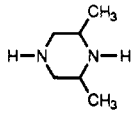
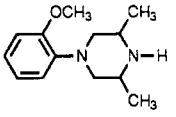
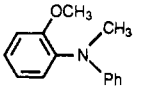
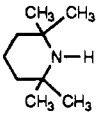
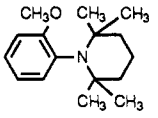
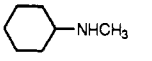
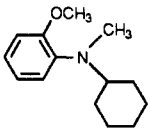
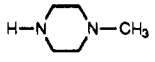
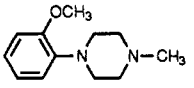
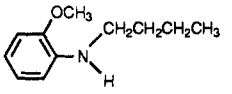
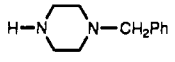
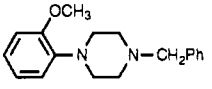
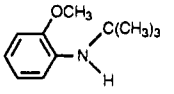
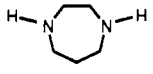
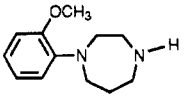
In an intramolecular variant of our amination, *N*-benzyl-*N*-lithio-2-(2-methoxyphenyl)ethylamine **23** is smoothly cyclized to the dihydroindole **24** (Scheme II). The primary analog 2-(2-methoxyphenyl)ethylamine did not undergo the intramolecular substitution under the standard conditions.

Another intramolecular reaction takes place when the amine **25** (or substituted with a methoxy group, compound **26**) shown in Scheme III is treated with *n*-butyllithium. The product **27** obtained in 20% yield (compound **28** where the methoxy group is present is obtained in 50% yield) is similar to the result of a Smiles rearrangement, yet the precursor lacks electron-withdrawing groups.[12]

Access to 1,2-diaminobenzene derivatives is also possible as shown in Scheme IV. Treatment of the reaction product **2** of veratrole and *N*-lithio-*N'*-methylpiperazine with 1.1 equiv of the same lithium amide results in substitution of the second methoxy group although the yield of **29** is only

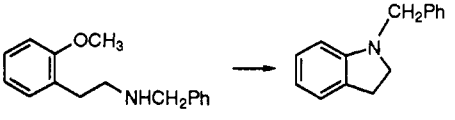
(10) Smith, P. A. S. *Org. React.* **1946**, *3*, 337.
(11) Hassner, A.; Munger, P.; Belinka, B. A., Jr. *Tetrahedron Lett.* **1982**, *23*, 699.
(12) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1970**, *18*, 99.

Table II. Reaction of Veratrole with Lithium Amides

entry	amine	product	yield (%)[a]	entry	amine	product	yield (%)
1		 **10**	60	11	NH_3		0
2		 **11**	70	12	$(CH_3)_2NH$	 **18**	90
3		 **12**	65	13	$(CH_3CH_2)_2NH$	 **19**	33
4		 **13**	45*	14	$((CH_3)_2CH)_2NH$		0
5		 **14**	75**	15	$PhCH_2NHCH_3$	 **20**	70
6		 **15**	70***	16	$PhNHCH_3$		0
7			0	17		 **21**	25
8		 **2**	75	18	$CH_3CH_2CH_2CH_2NH_2$	 **22**	28*
9		 **16**	65	19	$(CH_3)_3CNH_2$		0
10		 **17**	50*				

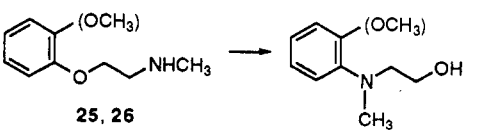
[a] (*) The product also contains some of the N-methylated amine analogue. (**) The least hindered N reacts mainly (9/1, by GC). (***) The least hindered N reacts exclusively.

Scheme II



23 24

Scheme III



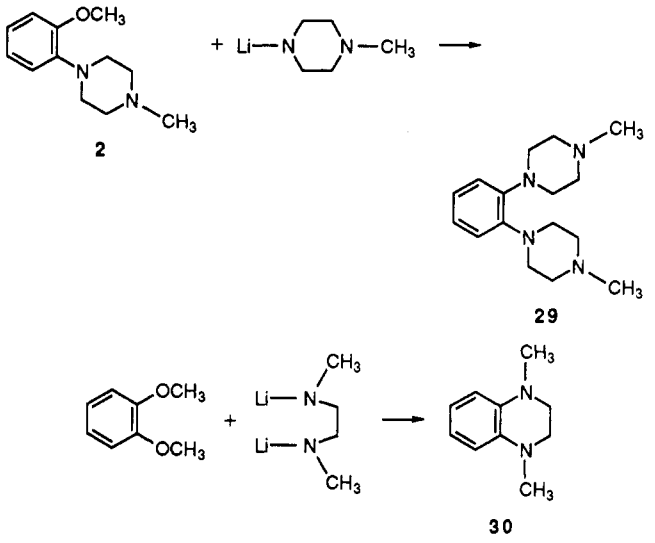
25, 26 27, 28

20%. Treatment of veratrole with the dilithiated *N,N'*-dimethylethanediamine results in the tetrahydroquinoxaline **30** in 60% yield.

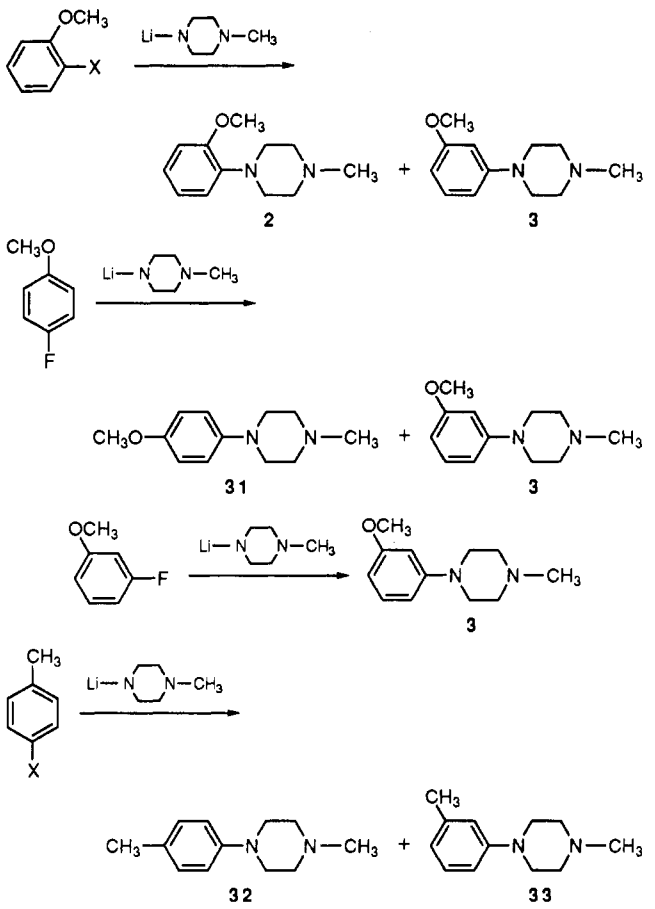
As already mentioned in the introduction, the pharmaceutically interesting class of electron-rich arylpiperazines is now accessible in a convenient and safe fashion.

Comparison with Halo Aromatics. In order to show the synthetic potential of alkoxy aromatics in the nucleophilic amination, especially with respect to regioselectivity, we have also submitted a range of aromatic halides to the reaction with *N*-lithio-*N'*-methylpiperazine. In all cases examined thus far where a methoxy group and a halogen atom are present it is the halogen atom which is substituted for the piperazine (this substitution takes place at rt in most cases, whereas the previously mentioned

Scheme IV



Scheme V



methoxy displacements require heating). The 2-haloanisoles show the following behavior (Scheme V): 2-fluoroanisole gives a 91% yield of a mixture of the 2- and 3-piperazinylanisole **2** and **3** (10/1 ratio, as determined by GC), 2-chloroanisole gives the same mixture in a 60% yield in a 1/3 ratio, whereas 2-bromoanisole gives the 3-isomer exclusively. Clearly, the bromide reacts through the benzyne mechanism; the chloride and the fluoride react through the benzyne mechanism as well as through a direct displacement reaction, the direct displacement becoming more provoked in 2-fluoroanisole. From 3-fluoroanisole the expected 3-piperazinylanisole **3** is formed exclusively and from 4-fluoroanisole a mixture of 3- and 4-piperazinylanisole **3** and **31** in a 4/5 ratio is formed. A similar trend is observed for 4-fluorotoluene and 4-bromotoluene on reaction with *N*-lithio-*N'*-methylpiperazine: both give a mixture of piperazinyltoluenes **32** and **33** but with 4-fluorotoluene a much larger amount of 4-isomer is obtained than with 4-bromotoluene (based on NMR).

From these experiments it can be concluded that the fluoride displacement, in contrast to chloride and bromide displacement, takes place with considerable selectivity, but that complete selectivity is not obtained due to the involvement of the benzyne mechanism, i.e. direct substitution takes place to a considerable extent with fluorides.

Further Experiments. In this section the influence of the solvent and the metal as well as some other relevant experiments will be discussed.

1. Solvent. Although most of the amination reactions were performed in refluxing THF, we have investigated a few other solvents for the nucleophilic amination. It appeared that the reactions can be performed as well in toluene, *tert*-butyl methyl ether, *N*-methylpiperazine, and tetramethylethylenediamine in yields comparable to the reaction in THF (these reactions were done for veratrole with *N*-methylpiperazine and *n*-butyllithium). Hence, the influence of the solvent is of relatively minor importance in our nucleophilic amination.

2. Metal. The reaction of veratrole with *N*-methylpiperazine in refluxing THF was investigated in the presence of sodium hydride, potassium hydride, and ethylmagnesium bromide (the piperazine being refluxed with the base for 1 h before veratrole was added and reflux was continued). With sodium hydride a 17% yield of the substitution product was obtained, with potassium hydride the yield was 9%, and with ethylmagnesium bromide the yield was 2%. A considerable amount of 2-methoxyphenol was also formed in these reactions. Hence, the nucleophilic amination proceeds well only with lithium amides.

3. When a mixture of 1 equiv of anisole and 1 equiv of (benzyloxy)benzene is treated with 1 equiv *N*-lithio-*N'*-methylpiperazine in THF there is recovered a 4/5 mixture of anisole and (benzyloxy)benzene (and 76% of *N*-methyl-*N'*-phenylpiperazine (**1**)). Hence, both aromatic ethers show almost equal reactivity in this reaction.

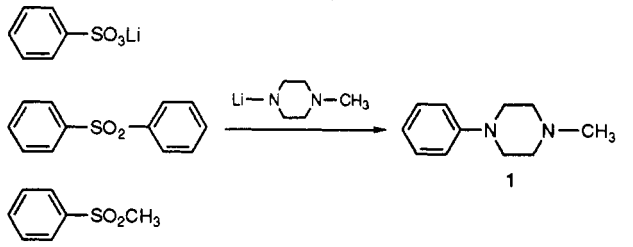
4. Treatment of a mixture of veratrole and anisole with *N*-lithio-*N'*-methylpiperazine gives a mixture of the two corresponding piperazines **2** and **1** in a GC ratio of 96/4, i.e. veratrole is much more reactive than anisole.

5. The following anisoles were very unreactive: 2-methylanisole, 4-methylanisole, and 4-methoxyanisole all gave very low yields of the substitution product with *N*-lithio-*N'*-methylpiperazine. This reactivity pattern was already mentioned by Cuvigny and Normant, and this pattern is also present in the ease of ortho-lithiation of these anisoles as compared to other anisoles.[13] In this respect, we have found no evidence that the methyl group in 2-methylanisole is lithiated under our reaction conditions (boiling with *N*-lithio-*N'*-methylpiperazine in THF followed by cooling and quenching with dimethyl disulfide; this did not lead to incorporation of a methylthio proup).

6. Brotherton and Bunnett reported that sodium amide in boiling piperidine cleaves arylsulfonic acids and arylsulfones to give arylpiperidines.[3] It appears that *N*-lithio-*N'*-methylpiperazine in THF behaves similarly. Lithium

(13) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

Scheme VI



1

benzenesulfonate gives a 75% yield of the phenylpiperazine 1, diphenyl sulfone gives a 93% yield, and methyl phenyl sulfone gives a 56% yield of the same piperazine (the latter compound was treated with 3 equiv of the lithium amide; with 1 equiv a yield only 10% was obtained) (Scheme VI).

Mechanism of the Nucleophilic Amination. Strong bases such as alkylmetals are known to dealkylate aromatic ethers[14,15] giving the phenolate ion as leaving group. In a few special cases the attack of organic bases is reversed, thus giving alkylaromatics and an alkoxide ion as the leaving group.[16] With metal amides a similar trend is observed: the attack of the amide anion can proceed in two ways giving either the phenolate ion or the alkoxide ion as the leaving group.[3,4,17] In our case, the attack of the lithium amide proceeds almost completely selective giving the alkoxide as the leaving group.

We assume that the SNAr mechanism is operative,[1] although definite proof cannot be given. The SRN1 mechanism[1] seems less plausible because the addition of radical scavengers (tetraphenylhydrazine or 2-methyl-2-nitrosopropane dimer)[18] to a mixture of veratrole and *N*-lithio-*N'*-methylpiperazine gave only a slight lowering of the yield of the substitution product. Also, the fact that only the outer methoxy group in 1,2,3-trimethoxybenzene is substituted seems to contradict the SRN1 mechanism, where the 2-methoxy group would also be expected to undergo substitution.

Although there seems to be a relationship between ease of ortho-lithiation and ease of substitution in our substrates (e.g. the reactive substrates anisole, veratrole, and fluorobenzene can all be ortho-lithiated,[19] whereas the unreactive substrates 4-methylanisole and 4-methoxyanisole are not easily lithiated), we have found no evidence that the ortho-lithiated species is an intermediate in our reactions. For instance, boiling for 5 min a mixture of veratrole (or 1,3-dimethoxybenzene) and *N*-lithio-*N'*-methylpiperazine in THF, followed by cooling and addition of dimethyl disulfide, did not lead to incorporation of a methylthio group.

We assume therefore that in the first step a complex is formed between the lithium amide and the aromatic ether, i.e. complexation of the lithium atom with the oxygen and nitrogen atoms, leading to structures similar to those proposed for the ortho-lithiation of aromatic ethers. In the next step the complexed lithium amide substitutes the alkoxy group.

(14) Morey, J.; Costa, A.; Deyá, P. M.; Suñer, G.; Saá, J. M. *J. Org. Chem.* **1990**, *55*, 3902 and refs cited therein.
(15) Kobrich, G.; Baumann, A. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 856.
(16) Richtzenhain, H.; Nippus, P. *Ber. Dtsch. Chem. Ges.* **1944**, *77*, 566. Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383. Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, 213.
(17) Bahtt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.
(18) Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7463.
(19) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

In conclusion, we have shown that the nucleophilic aminations discussed in this paper are a very practical method for the preparation of a wide variety of aromatic amines, several of which are difficultly accessible by other methods.

Experimental Section

General Remarks. All amination reactions were magnetically stirred and performed under an atmosphere of nitrogen. Tetrahydrofuran (THF) was stored over 4-Å sieves and used without further purification or freshly distilled from Na/benzophenone. All commercially available chemicals were obtained from Janssen Chimica or Aldrich and were used without further purification. The products obtained were purified by bulb-to-bulb distillation at 0.05 mbar. Unless stated otherwise, NMR spectra were recorded at 200 MHz in $CDCl_3$ with TMS as internal standard. 200-MHz ^1H NMR and ^{13}C NMR spectra were recorded on a Gemini 200 NMR spectrometer. 300-MHz ^1H NMR and ^{13}C NMR spectra were recorded on a Varian VXR 300S spectrometer. HRMS spectra were recorded on an AEI MS-902 spectrometer. Melting points were determined on a Mettler FP1 instrument and are uncorrected.

General Procedure. 1-(2-Methoxyphenyl)-4-methylpiperazine (2). A solution of *N*-methylpiperazine (2.2 mL, 20 mmol) in THF (30 mL) was stirred at 0 °C. A solution of 2.5 N *n*-butyllithium in hexanes (8.8 mL, 22 mmol) was added dropwise while a temperature of 0–10 °C was maintained. The reaction mixture was stirred at 0 °C for 30 min and at rt for 1 h. Then veratrole (2.6 mL, 20 mmol) was added to the clear, yellow solution. This mixture was refluxed overnight. After cooling, the mixture was poured into 100 mL of 2 N HCl and extracted with toluene (3 × 100 mL). The toluene layers were combined, dried over Na_2SO_4, filtered, and concentrated to give a mixture of veratrole and guaiacol (0.61 g, ratio by GC 2:1).

The acid layer was basified with 3 N NaOH and extracted with toluene (3 × 100 mL). The toluene layers were combined, dried over Na_2SO_4, filtered, and concentrated to give 3.1 g (75%) of 1-(2-methoxyphenyl)-4-methylpiperazine (2). Bulb-to-bulb distillation (125 °C, 0.05 mbar) gave a colorless oil that became a white solid upon standing: mp 33.0–34.8 °C; ^1H NMR δ 6.84–7.04 (m, 4H), 3.86 (s, 3H), 3.10 (m, 4H), 2.62 (m, 4H), 2.36 (s, 3H); ^{13}C NMR δ 152.05, 141.10, 122.67, 120.76, 118.01, 110.96, 55.18, 55.08, 50.44, 46.00.

Data for New Compounds. 1-(2,3-Dimethoxyphenyl)-4-methylpiperazine (4). Obtained as a colorless oil which solidifies upon standing: ^1H NMR (300 MHz) δ 6.88 (t, 1H), 6.50 (t, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.06 (m, 4H), 2.49 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (300 MHz) δ 153.15, 145.70, 141.28, 123.45, 110.76, 106.03, 58.90, 55.67, 55.42, 50.05, 45.93. Anal. Calcd for monohydrochloride, $C_{13}H_{21}N_2O_2Cl$: C, 57.22; H, 7.76; N, 10.27. Found: C, 56.95; H, 7.80; N, 10.31. Mp 244.0–244.4 °C.

1-Methyl-4-(2-thienyl)piperazine (8). Bulb-to-bulb distillation (120 °C, 0.05 mbar) gave a slightly yellow liquid which darkens upon standing: ^1H NMR δ 6.8–6.75 (dd, 1H), 6.6–6.55 (d, 1H), 6.15–6.1 (d, 1H), 3.2–3.1 (m, 4H), 2.6–2.5 (m, 4H), 2.33 (s, 3H); ^{13}C NMR δ 159.0, 125.9, 112.1, 105.2, 54.3, 51.4, 46.0; HRMS calcd for $C_9H_{14}N_2S$ 182.088, found 182.088.

***N,N*-Dimethyl-2-(4-methyl-1-piperazinyl)benzenamine (9).** Obtained as a colorless oil: ^1H NMR δ 6.95–6.85 (m, 4H), 3.1–3.2 (m, 4H), 2.8 (s, 6H), 2.5–2.6 (m, 4H), 2.35 (s, 3H); ^{13}C NMR δ 145.4, 143.9, 122.3, 121.6, 118.1, 117.8, 55.7, 48.9, 46.2, 41.6. Anal. Calcd for dihydrochloride·$^1/_3H_2O$, $C_{13}H_{23}N_3Cl_2·^1/_3H_2O$: C, 52.46; H, 7.99; N, 14.12. Found: C, 52.63; H, 8.13; N, 14.15. Mp 229.9–230.2 °C.

1-(2-Methoxyphenyl)-3-methylpiperazine (14). Obtained as a colorless oil: ^1H NMR δ 7.1–6.8 (m, 4H), 3.85 (s, 3H), 3.4–3.3 (m, 2H), 3.2–3.0 (m, 3H), 2.7–2.5 (m, 1H), 2.35–2.2 (m, 1H), 1.5 (s, 1H), 1.1 (d, 3H); ^{13}C NMR 152.1, 141.4, 122.7, 120.8, 118.1, 111.0, 58.5, 55.2, 51.1, 50.5, 46.1, 19.8. Anal. Calcd for dihydrochloride, $C_{12}H_{20}N_2OCl_2$: C, 51.62; H, 7.22; N, 10.03. Found: C, 51.51; H, 7.15; N, 9.95. Mp 189.0–189.5 °C.

1-(2-Methoxyphenyl)-1,4-diazepine (17). Obtained as a light yellow oil: ^1H NMR δ 7.0–6.8 (m, 4H), 3.8 (s, 3H), 3.4–3.25 (m, 4H), 3.1–2.95 (m, 4H), 2.0–1.8 (m, 2H), 1.75 (s, 1H); ^{13}C NMR

δ 151.6, 142.6, 120.8, 120.6, 118.1, 111.3, 55.9, 55.2, 52.5, 49.7, 47.7, 31.6. Anal. Calcd for dihydrochloride·$^2/_3H_2O$, $C_{12}H_{20}N_2OCl_2 \cdot {}^2/_3H_2O$: C, 49.70; H, 7.16; N, 9.66. Found: C, 49.77; H, 7.42; N, 9.59. Mp 146.4–146.9 °C.

***N*-Cyclohexyl-*N*-methyl-2-methoxybenzenamine (21).** Obtained as a colorless oil: ^1H NMR δ 7.0–6.8 (m, 4H), 3.85 (s, 3H), 3.25–3.1 (m, 1H), 2.7 (s, 3H), 1.8–1.0 (m, 10H); ^{13}C NMR δ 141.7, 136.4, 122.1, 120.9, 120.3, 111.1, 60.8, 55.3, 33.6, 29.2, 26.1. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.27; H, 9.80; N, 6.38.

***N*-Butyl-2-methoxybenzenamine (22).** Obtained as a colorless liquid: ^1H NMR δ 6.9–6.55 (m, 4H), 4.15 (bs, 1H), 3.8 (s, 3H), 3.1 (t, 2H), 1.7–1.55 (m, 4H), 1.55–1.3 (m, 4H), 0.95 (t, 3H); ^{13}C NMR δ 146.5, 138.3, 121.1, 115.9, 109.5, 109.1, 55.2, 43.2, 31.5, 20.2, 13.8. Anal. Calcd for hydrochloride $C_{11}H_{18}NOCl$: C, 61.25; H, 8.41; N, 6.49. Found: C, 61.25; H, 8.22; N, 6.49. Mp 143.6–146.9 °C.

1,2-Bis(4-methyl-1-piperazinyl)benzene (29). Obtained as white needles from acetone: mp 145.4–146.0 °C; ^1H NMR δ 7.0–6.9 (m, 4H), 3.2 (bs, 8H), 2.6 (bs, 8H), 2.35 (s, 6H); ^{13}C NMR δ 144.5, 122.6, 118.3, 55.8, 49.1, 46.2. Anal. Calcd for $C_{16}H_{26}N_4$: C, 70.03; H, 9.55; N, 20.42. Found: C, 70.04; H, 9.68; N, 20.19.

1-(4-Methylphenyl)-4-methylpiperazine (32). Obtained as a mixture with **33** only: ^1H NMR (after substraction of signals for **33**) δ 7.15–6.7 (AB, 4H), 3.2–3.1 (m, 4H), 2.6–2.5 (m, 4H), 2.3 (s, 3H), 2.25 (s, 3H); ^{13}C NMR δ 149.1, 129.3, 128.7, 116.0, 54.9, 49.3, 45.9, 20.1; HRMS calcd for a mixture of **32** and **33** $C_{12}H_{18}N_2$ 190.147, found 190.147.

1-(3-Methylphenyl)-4-methylpiperazine (33). Obtained as a colorless oil: ^1H NMR δ 7.2–7.0 (m, 1H), 6.75–6.65 (m, 3H), 3.19–3.13 (m, 4H), 2.55–2.49 (m, 4H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR δ 150.9, 138.2, 128.5, 120.2, 116.5, 112.8, 54.8, 48.8, 45.8, 21.5; HRMS calcd for $C_{12}H_{18}N_2$ 190.147, found 190.147.

2-(2-Methoxyphenyl)-*N*-(phenylmethyl)ethanamine (23). A solution of 2-(2-methoxyphenyl)ethylamine (7.5 g, 50 mmol) and benzaldehyde (5.3 g, 50 mmol) in ethanol (50 mL) was stirred at rt for 1.5 h. Then, $NaBH_4$ (2 g, 53 mmol) was added resulting in an exothermic reaction. The mixture was stirred at rt overnight and refluxed for 1 h. Acid/base treatment gave 9.2 g (76%) of a colorless liquid: ^1H NMR δ 7.3–7.1 (m, 7H), 6.9–6.8 (m, 2H), 3.8 (s, 2H), 3.75 (s, 3H), 2.85 (s, 4H), 1.5 (bs, 1H); ^{13}C NMR: δ 157.4, 140.3, 130.2, 128.2, 128.1, 127.9, 127.2, 126.6, 120.2, 110.1, 55.0, 53.6, 49.0, 30.6; HRMS calcd for $C_{16}H_{19}NO$ 241.147, found 241.147.