N-Alkyl-*N*-Cyclopropylanilines as Mechanistic Probes in the Nitrosation of *N*,*N*-Dialkyl Aromatic Amines

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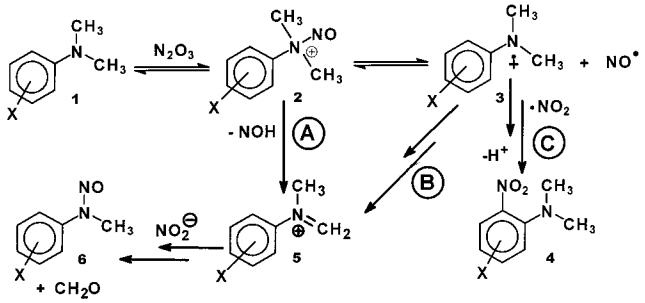
A group of *N*-cyclopropyl-*N*-alkylanilines has been synthesized, and their reaction with nitrous acid in aqueous acetic acid at 0 °C was examined. All compounds reacted rapidly to produce the corresponding *N*-alkyl-*N*-nitrosoaniline by specific cleavage of the cyclopropyl group from the nitrogen. The transformations were unaffected by the nature of the alkyl substituent (Me, Et, ^{i}Pr, Bn). The reaction of 4-chloro-*N*-2-phenylcyclopropyl-*N*-methylaniline with nitrous acid gave 4-chloro-*N*-methyl-*N*-nitrosoaniline (76%), cinnamaldehyde (55%), 3-phenyl-5-hydroxyisoxazoline (26%), and 5-(*N*-4-chlorophenylmethylamino)-3-phenylisoxazoline (8%). Both the selective cleavage of the cyclopropyl group from the aromatic amine nitrogen and nature of the products derived from the cyclopropane ring support a mechanism involving the formation of an amine radical cation. This step is followed by rapid cyclopropyl ring opening to produce an iminium ion with a C-centered radical which either combines with NO or is oxidized.

Introduction

While the reactions of secondary or primary aromatic amines with nitrous acid are quite well understood, the same cannot be said for *N*,*N*-dialkyl aromatic amines (exemplified by **1**, Scheme 1), whose transformations have remained perplexing to chemists over much of the history of organic chemistry. Generally, the formation of three or four different compounds are observed in these transformations: nitrosamines and or secondary amines formed by *N*-dealkylation reactions, aromatic nitro compounds, and, occasionally, aromatic C-nitroso compounds.[1,2] There are both health reasons related to the potential carcinogenic character of nitrosamines and practical reasons related to efficient industrial synthesis for understanding this chemistry.[3] Recently, we provided strong evidence for the existence of at least three linked competitive transformations which occur when *N*,*N*-dialkyl aromatic amines react with nitrous acid.[2] Key to this mechanistic scheme (Scheme 1) is the notion that a nitrosammonium ion **2** undergoes reversible homolysis to form a radical cation intermediate **3**. The latter species gives rise to both a nitrosamine **6** (path B) and a nitro compound **4** (path C), but the nitrosammonium ion also generates nitrosamines by competitive NOH elimination to **5** (path A), as shown.[4,5] An important piece of evidence supporting this hypothesis was the finding that *N*-alkyl-*N*-cyclopropylaromatic amines do not give any nitro compound but react with cyclopropyl ring opening. This evidence was taken to support the formation of a radical cation which was "trapped" by ring opening. The purpose of the research reported in this paper is to characterize the products arising from cyclopropyl ring opening and provide further evidence in support of the hypothesis that radical cations are involved in these nitrosation (and nitration) processes.

Scheme 1



Results

Synthesis of Aryl *N*-cyclopropylamines. *N*-Cyclopropylanilines **10** were prepared by refluxing the appropriate aniline derivative **7** and an excess of 1-bromo-1-ethoxycyclopropane **8** in the presence of triethylamine in dichloromethane (Scheme 2). The resulting *N*-(1-ethoxycyclopropyl)aniline derivatives **9** were reduced with $NaBH_4$ in the presence of BF_3•Et_2O.

N-(2-Phenylcyclopropyl)-*N*-methyl-4-chloroaniline **12** was prepared by cyclopropanation (diethyl zinc and diiodomethane) of the enamine **11** derived from the condensation of *N*-methyl-4-chloroaniline and phenylacetaldehyde (Scheme 3) in 71% overall yield.

Nitrosation Reactions. A solution of the appropriate *N*-cyclopropyl-*N*-alkylaniline in glacial acetic acid was nitrosated at 0 °C by the introduction of 2 equiv of an aqueous $NaNO_2$ solution. The progress of the reaction was monitored by TLC, and once the starting amine had been consumed, the mixture was neutralized and extracted into ether in order to obtain the product mixture. The reaction was usually complete within several min-

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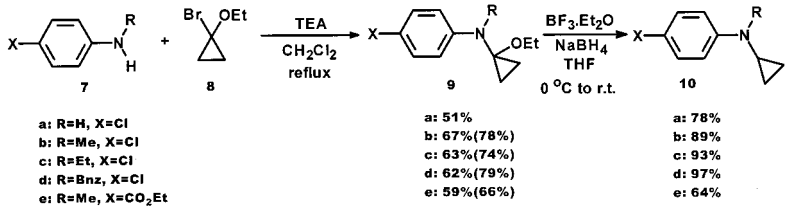
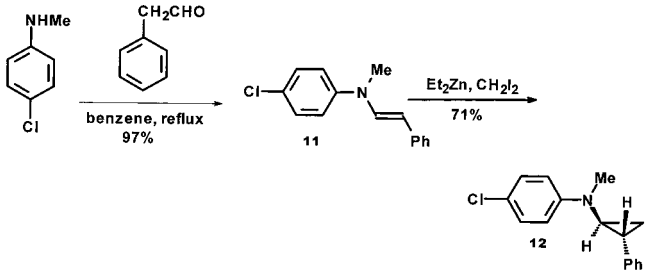
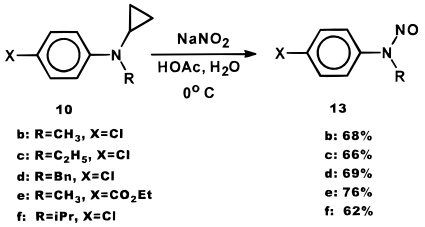
Scheme 2



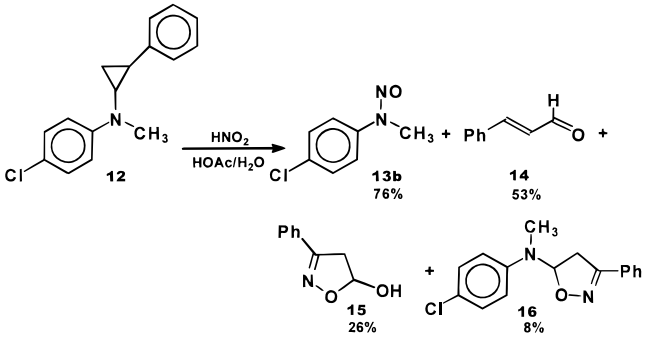
Scheme 3



Scheme 4



Scheme 5

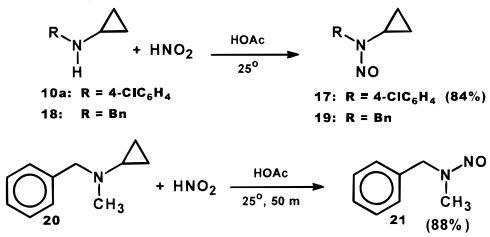


utes after the addition of $NaNO_2$. In each of these experiments the only nitrosamine product observed was the corresponding *N*-alkyl-*N*-nitrosoaniline **13** (see Scheme 4 for yields). In each case the cyclopropyl group was cleaved selectively from the nitrogen atom. No aromatic nitro products were observed.

To determine the nature of the products derived from the cyclopropyl ring, we used *N*-(2-phenylcyclopropyl)-*N*-methyl-4-chloroaniline (**12**). Attachment of the phenyl group to the cyclopropane ring assured the formation of products which could be more easily isolated and characterized than those derived from compounds with an unsubstituted cyclopropane ring. The nitrosation, conducted as described above, produced a mixture of four products which were separated by flash chromatography and characterized as follows.

Two of the compounds, *N*-nitroso-*N*-methyl-4-chloroaniline (**13b**) (76% yield; see Scheme 5) and cinnamaldehyde **14** (53% yield), are known compounds and were identified by a comparison of the spectral and chromatographic properties with authentic compounds. Compound

Scheme 6



16, produced in 8% yield, was assigned the structure of 5-(*N*-4-chlorophenylmethylamino)-3-phenylisoxazoline. This compound, having a formula $C_{16}H_{15}ClN_2O$, possesses an unsaturation index of 10, one more than the starting compound. Comparison of this formula with that of the starting material indicates that NO has been added and a proton lost. Moreover, the ^1H and ^{13}C NMR data clearly show that both aromatic rings have been retained without modification. Neither the IR spectrum nor the ^{13}C NMR spectrum are indicative of the presence of a carbonyl, but the presence of a ^{13}C peak at δ 155 and IR bands in the region 1487−1583 cm^{-1} are consistent with the presence of a C═N. In addition to the *N*-CH_3 peak in both the ^1H and ^{13}C NMR spectra, there are peaks supporting the presence of a CH−CH_2 group in which hydrogens of the methylene are nonequivalent, as they would be in a ring. On the basis of this information and mechanistic rationale described below, we have assigned structure **16** to this compound.

Compound **15** gave a formula $C_9H_9NO_2$, consistent with the addition of NO to cinnamaldehyde followed by the loss of a proton, and has been assigned the structure of 5-hydroxy-3-phenylisoxazoline. This is a known compound and both the melting point and the spectral properties of the substance isolated from our reaction are entirely consistent with those presented in the literature.[6]

Several control experiments were performed to examine the stability of the N-bound cyclopropyl group under the nitrosation conditions utilized by us. The nitrosation of 4-chloro-cyclopropylaniline (**10a**) gave 4-chloro-*N*-cyclopropyl-*N*-nitrosoaniline (**17**) in excellent yield (84%) (Scheme 6). *N*-Cyclopropylbenzylamine (**18**) also nitrosated cleanly to give the corresponding nitrosamine **19**. More surprising was the nitrosation of *N*-cyclopropyl-*N*-methylbenzylamine **20**, which gave benzylmethylnitrosamine (**21**) as the exclusive product in 88% yield at 25 °C.

Discussion

As indicated in the Introduction, nitrosation of *N*,*N*-dialkyl aromatic amines occurs by three competing pathways: two of which give the nitrosamine, and the

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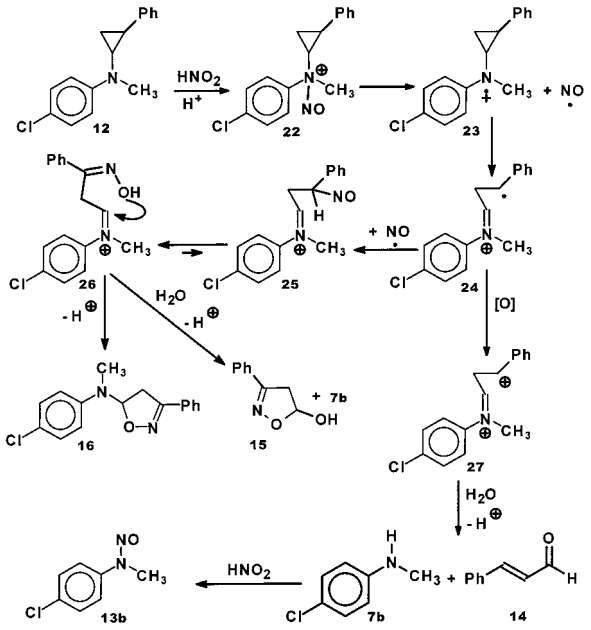
third produces an *o*-nitro compound. In this context, the data presented here exhibit several remarkable features. The results presented in Scheme 4 show that, regardless of the other N-bound substitutent, all compounds give only the nitrosamine produced by the loss of the cyclopropyl group. The yields, determined for the isolated products, are relatively consistent from compound to compound and show that the size of the *N*-alkyl substitutent has little effect on the reaction course. Moreover, when compared with other tertiary amine nitrosation reactions,[2,4,5] even those of similar compounds, the *N*-cyclopropylanilines react very rapidly as evidenced by the complete consumption of starting material within minutes at 0 °C. These data, as well as the nature of the cyclopropyl ring derived products, are completely consistent with the hypothesis that these tertiary amine dealkylation reactions are occurring exclusively through a radical cation (path B of Scheme 1).

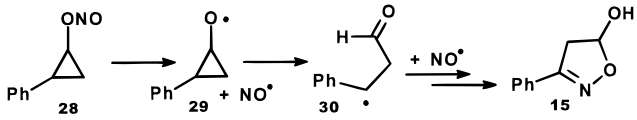
Extensive documentation demonstrates that the formation of a radical on an atom to which a cyclopropyl ring is attached results in the rapid opening of the three-membered ring.[7] The rate of cyclopropyl ring opening has been independently determined for several systems where the cyclopropyl group is attached to a carbon centered radical and serves as a "radical clock" for the timing of competitive intramolecular processes.[8] Rapid cyclopropyl ring opening also occurs when a radical cation or radical is centered on an attached N-atom and has been used extensively to detect amine radical cation formation in enzymatic amine oxidations[9−12] and related chemical model processes.[13,14] We have produced evidence that *N*,*N*-dialkyl aromatic amine nitrosation occurs by the reversible homolysis of the nitrosammonium ion **2** (Scheme 1) to produce the radical cation **3** and NO.[2] In the case of the *N*-cyclopropylanilines, however, the opening of the three-membered ring occurs so rapidly as to preclude either recombination of the radical cation and NO or its reaction with NO_2 to give a nitro compound **4**. Thus, the opening of the cyclopropyl ring is envisioned to kinetically force the transformation exclusively in one direction, the regioselective removal of the cyclopropyl substitutent from the amine nitrogen. In other work in our laboratory, we have shown that the nature of the *N*-alkyl group affects the rate of *N*,*N*-dialkylaniline nitrosation reactions. *N*-Benzyl and *N*-isopropyl groups retard the reaction rate. These observations led us to the hypothesis that larger *N*-alkyl groups induced rotation around the aryl C to N bond through steric hindrance in such a way as to diminish N-p-π electron donation to the aromatic ring. Such a phenomenon is not manifested here, since the reactions are independent of the size of the *N*-alkyl substituent.

The nature of the reaction products observed from the nitrosation of *N*-(2-phenylcyclopropyl)-*N*-methyl-4-chloroaniline (**12**) is also consistent with generation of a

Scheme 7



Scheme 8



radical cation (**23**) followed by rapid ring opening to produce the separated cation radical **24**, as shown in Scheme 7. This reactive intermediate is then consumed by two competitive pathways. Oxidation of **24** by the nitrous acid medium results in **27**. Nitrous acid is well-known to consist of a mixture of nitrogen species, the relative concentrations of which are dependent upon pH, temperature, [H_2O], and the nature of the anion derived from the acid used to generate the nitrous acid from sodium nitrite. Several of these nitrogen species (NO^+, NO_2, and N_2O_3) are known to be effective oxidants as well as electrophiles.[2] Under our reaction conditions the most probable oxidant is N_2O_3, which reacts with **24** ($R^\bullet$) to give $NO^\bullet$, NO_2^-, and the carbocation **27**, which is converted into cinnamaldehyde (**14**) and the secondary amine **7b** by proton loss followed by hydrolysis of the iminium ion. Nitrosation of the amine coproduct of this hydrolysis, **7b**, forms the nitrosamine **13b**. In the other pathway, the radical center of **24** reacts with NO to generate **25**, which isomerizes to the oximinoiminium ion **26**. The main reaction of this oxime involves hydrolysis to the secondary amine **7b** and the isoxazoline **15**. A similar process generates the isoxazoline **16**.

The conversion of **23** to **15** and **16** has literature precedent. DePuy and colleagues[6] examined the thermolysis and photolysis of a series of cyclopropyl nitrites. In two cases, where phenyl-substituted cyclopropyl nitrites were employed, they observed the formation of isoxazolines. In one case, as shown in Scheme 8, the product was **15**. In every case examined by them, the carbon radical produced by the opening of the cyclopropane ring reacted with NO to form a nitrogen containing product. Another interesting feature of this chemistry, which parallels our observation, is the unexpectedly rapid homolytic decomposition of the cyclopropyl nitrites, e.g. **28**, at low temperatures (0−5 °C). Simple alkyl nitrites

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undergo homolytic scission of the N−O bond above 80 °C at measurable rates. The influence of substituents on homolytic bond scission remains an intriguing problem. DePuy et al. attributed the rapid rate of cyclopropyl nitrite homolysis to a concerted homolysis of the O−N and C−C bonds. The ability of a remote substitutent to influence decomposition rates by the synchronous scission of two or more bonds, however, has been questioned more recently.[15] The high reactivity in this system as well as ours could be explained by reversible homolytic scission to generate NO. In systems without cyclopropyl ring substituents, the recombination with NO occurs. In systems containing the cyclopropyl ring adjacent to the radical site, rapid ring opening precludes attack at the original atom of NO attachment. Despite the inherent logic of such an argument, it is intuitively difficult to imagine that normal alkyl nitrites, for example, are undergoing undetected reversible homolysis at temperatures as low as 25 °C.

In this context, the results of our "control reactions" are particularly interesting. Given the known reactivity of cyclopropane rings toward electrophiles, we considered that the attack of NO^+ (or equivalent) on a cyclopropyl ring bond to generate a stabilized iminium ion, rather than initial *N*-nitrosation, could explain our observations. The nitrosation of 4-chloro-*N*-cyclopropylaniline (**10a**) under the same conditions used for the tertiary amines resulted in its smooth conversion to 4-chloro-*N*-cyclopropyl-*N*-nitrosoaniline (**17**). A similar observation was made for the nitrosation of *N*-cyclopropylbenzylamine (**18**). The nitrosation smoothly produces benzylcyclopropylnitrosamine (**19**) in high yield, yet the nitrosation of *N*-cyclopropyl-*N*-methylbenzylamine (**20**) gives exclusively benzylmethylnitrosamine (**21**) at 25 °C. There are several notable features associated with these observations. The ability of the *N*-cyclopropyl secondary amines to be efficiently converted into their respective nitrosamines argues against either direct nitrosation of the cyclopropyl ring or the involvement of radical cations in these processes. It has been reported that radical cations can be formed in the nitrosation reactions of both primary and secondary aromatic amines,[16,17] the oxidation potentials of which are certainly less positive than most aliphatic amines. But initial *N*-nitrosation must be followed by rapid proton loss to give the nitrosamine rather than reversible homolysis to generate a radical cation and NO, which would certainly lead to cyclopropyl ring opening.

The most surprising result involves the very rapid nitrosation of the tertiary amine *N*-cyclopropyl-*N*-methylbenzylamine (**20**), which results in the exclusive cleavage of the cyclopropyl ring from the nitrogen. The nitrosation of *N*,*N*-dimethylbenzylamine occurs only at a measurable rate at temperatures above 50 °C and results in cleavage of both methyl and benzyl groups from N.[18] We had thought the latter process to occur exclusively by NOH elimination (see Scheme 1), but the specific removal of the cyclopropyl ring from **20**, coupled with its very rapid nitrosation, suggests that radical cations can be involved in these processes as well. This possibility is being probed by further experimentation.

Finally, although we have shown the fate of the cleaved cyclopropyl group in the case where it bears a phenyl substituent (**12**), it is possible that this substituent influences the chemistry because it is known to increase the rate of cyclopropane ring opening in carbon systems.[8] Because of their low molecular weight and water solubility, products derived from the opening of the unsubstitued cyclopropyl group are difficult to detect in our system. It is unlikely, however, that the fundamental nature of the operative mechanistic process, generation of the radical cation by the path shown in Scheme 1 and the subsequent opening of the cyclopropyl group, is changed by H for phenyl substitution on the three-membered ring.

Conclusion

The data presented here strongly support our hypothesis that the nitrosation of *N*,*N*-dialkyl aromatic amines involves the reversible homolysis of a nitrosammonium ion or an equivalent electron-transfer process. It is difficult to explain both the regiospecific cleavage of the cyclopropane ring from the nitrogen atom and the nature of the products produced from **12** without invoking the formation of an amine radical cation. The data and interpretation presented here provide additional support for the mechanistic hypothesis presented in Scheme 1, which arose from our prior work.

Experimental Section

The Synthesis of Secondary *N*-Alkylanilines and Their Nitrosamines. *N*-Methyl- (**7b**), *N*-ethyl- (**7c**), and *N*-benzyl-4-chloroaniline (**7d**), as well as ethyl 4-methylaminobenzoate (**7e**) and their corresponding nitrosamines (**13b**−**e**), are all known compounds. Amines were prepared by the reduction of their respective amides with BH_3·THF and the nitrosamine by acidic nitrosation.

4-Chloro-*N*-cyclopropylaniline (10a). *N*-(1-Ethoxycyclopropyl)-4-chloroaniline was obtained by stirring 1 g (7.8 mmol) of 4-chloroaniline with 2.6 g (15.78 mmol) of 1-bromo-1-ethoxycyclopropane in the presence of excess triethylamine in refluxing dichloromethane for 48 h. Workup and chromatographic purification (15% ethyl acetate in hexane) gave the product as a white solid (mp 46−47 °C) in 51% yield (0.84 g) which was used directly in the reduction step without additional compositional characterization beyond the spectral data listed. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (d, 2H, J = 8.7 Hz), 6.79 (d, 2H, J = 8.7 Hz), 4.78 (br s, 1H), 3.54 (q, 2H, J = 7.0 Hz), 1.11 (br t, 5H, J = 7.0 Hz), 0.85 (dd, 2H, J = 4.7, 6.6 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 144.06, 128.86, 123.07, 115.29, 68.59, 60.93, 15.29, 14.87.

Using the reduction procedure described in general below, 800 mg (3.78 mmol) of *N*-(1-ethoxycyclopropyl)-4-chloroaniline dissolved in 2 mL of dry THF was added dropwise to a stirring solution of 287 mg (7.58 mmol) of $NaBH_4$ and 1.01 g (7.58 mmol) of BF_3·Et_2O in 6 mL of THF at 0 °C under an atmosphere of nitrogen. After stirring at rt for 38 h, TLC indicated reaction completion. Workup and chromatographic purification (10% ethyl acetate in hexanes) afforded the desired product as a colorless oil in 78% yield (470 mg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (dt, 2H, J = 3.3, 8.7 Hz), 6.71 (dt, 2H, J = 3.3, 8.7 Hz), 4.15 (br s, 1H), 2.40−2.37 (m, 1H), 0.74−0.71 (m, 2H), 0.51−0.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 147.20, 128.89, 122.31, 114.17, 25.27, 7.40; IR (neat) 3405m cm^{-1}; MS (70 eV) 169 ($(M + 2)^+$, 24), 168 ($(M + 1)^+$, 30), 167 (M^+, 75), 166 (77), 140 (63), 138 (88), 132 (100), 131 (52), 130 (90), 111 (50), 77 (31), 75 (52), 51 (23). Anal. Calcd for $C_9H_{10}NCl$: C, 64.48; H, 6.01; N, 8.36. Found C, 64.62; H, 5.89; N, 8.54.

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***N*-Cyclopropylbenzylamine (18).** To a stirring solution of 10 g (175 mmol) of cyclopropylamine (purchased from Aldrich) and 3.2 g (30 mmol) of benzaldehyde and 1.25 g (20 mmol) of $NaCNBH_3$ in 50 mL of methanol was added 30 mL of 2.25 M HCl in MeOH dropwise at rt. The resulting solution was allowed to stir for 72 h without monitoring. The reaction mixture was treated with 15 mL of 3 N NaOH solution and extracted in 100 mL of ether. The ether layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure on a rotary evaporator. The resulting colorless oil was further purified by flash column chromatography using 100% hexanes as an eluent. The pure product was obtained as a colorless oil in 78% yield (3.44 g): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.30 (m, 4H), 7.27−7.22 (m, 1H), 3.84 (s, 2H), 2.19−2.13 (m 1H), 1.81 (br s, 1H), 0.46−0.42 (m, 2H), 0.41−0.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 140.56, 128.29, 128.12, 126.76, 53.67, 29.98, 6.41; IR (neat) 3317w, 3276w cm^{-1}; MS (70 eV) 146 (M^+, 22), 132 (19), 92 (11), 91 (100), 65 (19). Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.51. Found C, 81.70; H, 9.10; N, 9.23.

The Synthesis of *N*-Cyclopropyl-*N*-Alkylanilines. General Procedure for the Alkylation of Aniline Derivatives with 1-Ethoxy-1-bromocyclopropane.[19,20] In an oven-dried reaction flask equipped with a Teflon-sealed stirring bar and a reflux condenser with a drying tube ($CaCl_2$), the appropriate aniline derivative **7**, an excess (1.5−2 mmol equiv) of 1-bromo-1-ethoxycyclopropane **8**, and triethylamine (1.5−2 mmol equiv) were mixed in dichloromethane (2 M solution with respect to the aniline substrate). The resulting mixture was allowed to stir at reflux for 24−72 h. The progress of the reaction was monitored by TLC. When the reaction was completed, the mixture was diluted with dichloromethane (3−5 mL/mmol of amine), washed with water (2 × 3 mL/mmol), and washed once with brine. The aqueous washes were back-extracted with an equal amount of dichloromethane. The two organic layers were combined and dried over anhydrous $MgSO_4$ or Na_2SO_4. Filtration and removal of the solvent under reduced pressure on a rotary evaporator followed by flash column chromatographic purification afforded the desired products. For a representative example of this procedure, see the alkylation of 4-chloro-*N*-methylaniline **7b** below.

General Procedure for the Reduction of *N*-(1-Ethoxycyclopropyl)anilines 9. Reduction according to the procedure of Kang[21] proceeded as follows. In an oven-dried reaction flask equipped with a stirring bar and a rubber septa, the appropriate *N*-(1-ethoxycyclopropyl)aniline derivative (1 mmol equiv) dissolved in freshly distilled THF (1 mL/mmol of substrate) was added dropwise to a stirring mixture of $NaBH_4$ (2 equiv) and BF_3·Et_2O (2 equiv) in dry THF (1 mL/mmol equiv) at 0 °C (the $NaBH_4$−BF_3·Et_2O mixture was stirred for 30−45 min before the addition of the substrate at 0 °C). The resulting solution was allowed to slowly warm to room temperature with stirring, and continued the stirring until reaction completion. The progress of the reaction was monitored by TLC. Once completed, the reaction mixture was carefully quenched with water and extracted in diethyl ether (5 mL/mmol) by washing with 3 × 20 mL of H_2O and 1 × 20 mL of brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residues were purified by flash column chromatography. For a representing procedural example, see the reduction of 4-chloro-*N*-(1-ethoxycyclopropyl)-*N*-methylaniline **9b** below.

4-Chloro-*N*-cyclopropyl-*N*-methylaniline (10b). In a flame-dried reaction flask equipped with a stirring bar and a reflux condenser with a drying tube, 2.0 g (14.12 mmol) of *N*-methyl-4-chloroaniline[2] **7b**, 3.5 g (21.18 mmol) of 1-ethoxy-1-bromocyclopropane, and 2.14 (21.18 mmol) of triethylamine were all dissolved in 7 mL of dry dichloromethane under nitrogen atmosphere. The resulting mixture was allowed to reflux with stirring for 65 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with 45 mL of dichloromethane and rinsed with 2 × 30 mL of water and once with 20 mL of saturated aqueous sodium chloride solution. The aqueous washes were back-extracted with 45 mL of CH_2Cl_2. The two organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure on a rotary evaporator. The resulting residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to give 4-chloro-*N*-(1-ethoxycyclopropyl)-*N*-methylaniline **9b** as a colorless oil in 67% yield (78% corrected): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (dt, 2H, J = 3.3, 9.2 Hz), 6.91 (dt, 2H, J = 3.3, 9.2 Hz), 3.51 (q, 2H, J = 7.0 Hz), 3.06 (s, 3H), 1.22 (br s, 2H), 1.11 (t, 3H, J = 7.0 Hz), 0.90 (br d, 2H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.2, 128.48, 122.49, 114.69, 75.09, 62.24, 37.94, 16.42, 15.42.

In an oven-dried reaction flask equipped with a stirring bar and a rubber septa, 671 mg (17.73 mmol) of $NaBH_4$ was suspended in 15 mL of dry THF. The solution was cooled to 0 °C and 2.66 g (17.73 mmol) of BF_3·Et_2O was added via a syringe under nitrogen atmosphere. The mixture was stirred at 0 °C for 45 min, and 2.0 g (8.86 mmol) of *N*-methyl-*N*-(1-ethoxycyclopropyl)-4-chloroaniline **9b**, dissolved in 3 mL of dry THF was added dropwise via a gastight syringe. The reaction mixture was allowed to slowly warm to room temperature with stirring and continued to stir at rt for an additional 6 h. TLC, then, indicated reaction completion. The reaction was carefully quenched with water and extracted in 40 mL of diethyl ether by washing with 3 × 20 mL of H_2O and 1 × 20 mL of brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography purification (3% ethyl acetate in hexanes) afforded the desired product **10b** as a colorless oil in 89% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dt, 2H, J = 3.3, 9.2 Hz), 6.9 (dt, 2H, J = 3.3, 9.2 Hz), 2.94 (s, 3H), 2.53 (m, 1H), 0.81 (m, 2H), 0.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.39, 128.54, 122.19, 114.80, 39.07, 33.30, 9.07; MS (70 eV): 183 ($(M + 2)^+$, 30), 182 ($(M + 1)^+$, 36), 181 (M^+, 100), 180 (81), 168 (24), 166 (82), 154 (30), 146 (61), 145 (47), 144 (69), 140 (29), 138 (58), 131 (26), 130 (41), 127 (23), 125 (65), 113 (27), 110 (80), 77 (33), 75 (73), 70 (34), 63 (20), 65 (37), 51 (31). Anal. Calcd for $C_{10}H_{12}ClN$: C, 66.11; H, 6.66; N, 7.71. Found C, 66.29; H, 6.52; N, 7.52.

4-Chloro-*N*-cyclopropyl-*N*-ethylaniline (10c). The intermediate *N*-(1-Ethoxycyclopropyl)-*N*-ethyl-4-chloroaniline **(9c)** was prepared by stirring 1 g (6.42 mmol) of 4-chloro-*N*-ethylaniline [22] **7c** and 2 g (12.12 mmol) of 1-bromo-1-ethoxycylopropane in refluxing CH_2Cl_2 in the presence of excess Et_3N for 96 h according to the reaction conditions described above. The crude reaction mixture was purified by column chromatography on silica gel (eluted with 4% ethyl acetate in hexanes) to give the product as a colorless oil in 63% yield (74% corrected): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (d, 2H, J = 9.0 Hz), 6.91 (d, 2H, J = 9.0 Hz), 3.56 (q, 2H, J = 7.0 Hz), 3.47 (q, 2h, J = 7.0 Hz), 1.19 (br s, 2H), 1.13 (t, 3H, J = 7.0 Hz), 1.10 (t, 3H, J = 7.0 Hz), 0.94 (br d, 2H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 144.83, 128.53, 122.15, 115.11, 75.06, 61.93, 45.05, 15.41, 13.69.

To a stirring solution of $NaBH_4$ (475 mg; 12.5 mmol) and BF_3·Et_2O (1.78 g; 12.5 mmol) in 10 mL of THF at 0 °C was added dropwise 1.5 g (6.26 mmol) of *N*-(1-ethoxycyclopropyl)-*N*-ethyl-4-chloroaniline **5c** dissolved in 3 mL of THF, and the resulting solution was allowed to stir at rt for 8 h. Standard aqueous workup and chromatographic purification (4% ethyl acetate in hexanes) provided the product as a colorless oil in 96% yield (1.17 g): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.15 (dt, 2H, J = 3.3, 9.1 Hz), 6.88 (dt, 2H, J = 3.3, 9.1 Hz), 3.43 (q, 2H, J = 7.0 Hz), 2.42−2.34 (m, 1H), 1.07 (t, 3H, J = 7.0 Hz), 0.84−0.79 (m, 2H), 0.59−0.53 (m 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 147.87, 128.62, 121.95, 115.41, 45.39, 30.91, 11.36, 8.90; MS (70 eV) 197 ($(M + 2)^+$, 19), 196 ($(M + 1)^+$, 16), 195 (M^+, 57),

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194 (31), 180 (37), 168 (21), 166 (57), 151 (20), 145 (21), 144 (40), 139 (41), 138 (97), 131 (23), 130 (55), 125 (37), 113 (32), 110 (100), 77 (24), 76 (21), 75 (72), 70 (69), 56 (46), 51 (22). Anal. Calcd for $C_{11}H_{14}ClN$: C, 67.51; H, 7.21; N, 7.16: Found: C, 67.27; H, 6.98; N, 6.91.

4-Chloro-*N*-benzyl-*N*-cyclopropylaniline (10d). The intermediate *N*-(1-ethoxycyclopropyl)-*N*-benzyl-4-chloroaniline **(9d)** was prepared by stirring 2.6 g (11.94 mmol) of 4-chloro-*N*-benzylaniline [23] **7d** and 2.9 g (17.9 mmol) of 1-bromo-1-ethoxycylopropane in refluxing CH_2Cl_2 in the presence of excess Et_3N according to the reaction conditions described above. After stirring at reflux for 96 h, the reaction was stopped and worked up. The crude reaction mixture was purified by column chromatography on silica gel (eluted with 5% ethyl acetate in hexanes) to give the product as a white solid (mp 103−104 °C) in 62% yield (79% corrected): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (t, 2H, J = 7.2 Hz), 7.20 (t, 1H, J = 7.2 Hz), 7.10 (dt, 2H, J = 3.3, 9.1 Hz), 7.0 (br d, 2H, J = 7.2 Hz), 6.86 (dt, 2H, J = 3.3, 9.1 Hz), 4.82 (br s, 2H), 3.56 (q, 2H, J = 7.0 Hz), 1.17 (br s, 2H), 1.14 (t, 3H, J = 7.0 Hz), 0.95 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 145.04, 138.78, 128.73, 128.51, 126.83, 125.25, 122.91, 115.60, 75.29, 62.18, 55.78, 15.42.

Using the same reduction procedure, 1 g (3.31 mmol) of *N*-(1-ethoxycyclopropyl)-*N*-benzyl-4-chloroaniline **9d** was reduced with $NaBH_4$ (250 mg; 6.62 mmol) in the presence of $BF_3{\cdot}Et_2O$ (884 mg (6.62 mmol) according to the reduction procedure described earlier. The reaction was completed after stirring at room temperature for 3 h. Workup and chromatographic purification on silica gel (3% ethyl acetate in hexanes) gave the product **10d** as a colorless oil in 98% yield: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.31−7.19 (m, 3H), 7.14−7.08 (m, 4H), 6.82 (dt, 2H, J = 3.3, 9.0 Hz), 4.58 (s, 2H), 2.62−2.54 (m, 1H), 0.86−0.79 (m, 2H), 0.7−0.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 148.38, 139.35, 128.61, 128.53, 126.77, 126.29, 122.31, 115.08, 56.15, 32.80, 8.96; MS (70 eV) 259 ((M + 2)$^+$, 34), 258 ((M + 1)$^+$, 40), 257 (M$^+$, 100), 256 (69), 228 (27), 166 (41), 138 (38), 132 (72), 110 (24), 91 (97). Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.56; H, 6.25; N, 5.43. Found C, 74.57; H, 6.10; N, 5.55.

Ethyl 4-(*N*-Cyclopropyl-*N*-methyl)aminobenzoate (10e). The intermediate ethyl 4-*N*-(1-ethoxycyclopropyl)methylaminobenzoate **9e** was prepared by stirring 1 g (5.5 mmol) of ethyl 4-methylaminobenzoate[24] **7e** and 1.8 g (10.9 mmol) of 1-bromo-1-ethoxycylopropane in refluxing CH_2Cl_2 in the presence of excess Et_3N. The reaction was stopped after refluxing for 88 h. Workup and purification by column chromatography on silica gel (eluted with 5% ethyl acetate in hexanes) afforded the product as a colorless oil (solidifies in the freezer) in 59% yield (66% corrected): ^{1}H NMR ($CDCl_3$, 125 MHz) δ 7.93 (dt, 2H, J = 2.6, 9.0 Hz), 6.99 (dt, 2H, J = 2.6, 9.0 Hz), 4.32 (q, 2H, J = 7.1 Hz), 3.52 (q, 2H, J = 7.0 Hz), 3.16 (s, 3H), 1.36 (t, 3H, J = 7.1 Hz), 1.26 (br s, 2H), 1.11 (t, 3H, J = 7.0 Hz), 0.94 (br d, 2H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 166.86, 151.35, 130.67, 119.33, 112.74, 75.00, 62.35, 60.10, 37.89, 15.34, 14.39.

Ethyl 4-*N*-cyclopropyl-*N*-methylaminobenzoate (10e) was prepared by subjecting 500 mg (1.9 mmol) of 4-*N*-(1-ethoxycyclopropyl)methylaminobenzoate **9e** to the reduction procedure described above (43 h) using $NaBH_4$ (3.8 mmol) in the presence of $BF_3{\cdot}Et_2O$ (3.8 mmol). Purification of the resulting residue on silica gel (column chromatography; 15% ethyl acetate in hexanes) afforded the desired product **10e** as a white solid (mp 27−28 °C) in 64% yield (271 mg): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.92 (dt, 2H, J = 2.8, 9.0 Hz), 6.90 (dt, 2H, J = 2.8, 9.0 Hz), 4.32 (q, 2H, J = 7.1 Hz), 3.03 (s, 3H), 2.56 (s, 2H), 2.62−2.54 (m, 1H), 1.36 (t, 3H, J = 7.1 Hz), 0.91−0.84 (m, 2H), 0.68−0.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 167.01, 153.95, 130.84, 118.54, 112.28, 60.11, 38.37, 33.04, 14.45, 9.22; IR (thin film) 1696s, 1606s, 1277s, 1181s cm^{-1}; MS (70 eV) 220 ((M + 1)$^+$, 13), 219 (M$^+$, 100), 218 (64), 204 (43), 190 (42), 176 (17), 174 (56), 149 (25), 146 (57), 145 (24), 144 (44), 132 (28), 131 (33), 130 (26), 105 (24), 104 (22), 77 (27), 70 (29), 65 (20), 56 (25). Anal. Calcd for $C_{13}H_{17}ClNO_2$: C, 71.20; H, 7.81; N, 6.39. Found C, 71.13; H, 7.66; N, 6.14.

4-Chloro-*N*-cyclopropyl-*N*-isopropylaniline (10f). To a stirring solution of 1.1 g (6.56 mmol) of *N*-cyclopropyl-4-chloroaniline **10a** and 1.9 g (32.8 mmol) of acetone in 10 mL of methanol were added 630 mg (10 mmol) of $NaCNBH_3$ and 10 mL of 2.25 M of HCl in methanol in succession. The resulting mixture was allowed to stir at room temperature for 4 days. Workup and extraction in ether followed by chromatographic separation (3% ethyl acetate in hexanes) afforded the desired product **10f** in 24% yield as a colorless oil. The starting amine was recovered in 47% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (d, 2H, J = 9.0 Hz), 6.92 (d, 2H, J = 9.0 Hz), 3.84 (septet, 1H, J = 6.7 Hz), 2.27−2.23 (m, 1H), 1.24 (d, 6H, J = 6.7 Hz), 0.77 (m, 2H), 0.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 150.11, 128.23, 123.20, 118.85, 54.58, 26.32, 20.76, 9.05; MS (70 eV) 211 ((M + 2)$^+$, 15), 210 ((M + 1)$^+$, 10), 209 (M$^+$, 54), 196 (30), 194 (87), 180 (23), 166 (52), 153 (38), 152 (34), 151 (34), 140 (37), 139 (21), 138 (100), 131 (27), 130 (49), 125 (48), 113 (27), 110 (80), 84 (49), 75 (53); Anal. Calcd for $C_{12}H_{16}ClN$: C, 68.72; H, 7.70; N, 6.68. Found C, 68.70; H, 7.67; N, 6.47.

***N*-Cyclopropyl-*N*-methylbenzylamine (20).** This compound was obtained by reductive amination of formaldehyde with *N*-cyclopropylbenzylamine. To a stirring solution of *N*-cyclopropylbenzylamine **18** (2.5 g; 16.99 mmol), formaldehyde (2.43 g of 37% HCHO in water; 900 mg, 30 mmol HCHO), and $NaCNBH_3$ (1.07 g, 16.99 mol.) in 30 mL of methanol was added dropwise 10 mL of 2.25N HCl in MeOH. The resulting mixture was allowed to stir at rt for 48 h. The reaction mixture was treated with 10 mL of 3 N NaOH solution and extracted in 50 mL of ether. The aqueous layer was extracted again with 50 mL of ether, and the two layers were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure on a rotary evaporator. The resulting oil was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to give the desired product **20** as a colorless oil in 68% yield (84% based on recovered starting amine): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.22 (m, 5H), 3.66 (s, 2H), 2.25 (s, 3H), 1.72−1.68 (m, 1H), 0.48−0.45 (m, 2H), 0.44−0.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 138.48, 129.36, 128.04, 126.83, 62.24, 41.91, 38.47, 7.10; MS (70 eV) 161 (M$^+$, 15), 160 (55), 146 (17), 132 (12), 91 (100), 70 (29), 65 (29). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.68. Found C, 81.73; H, 9.29; N, 8.54.

The Synthesis of 4-Chloro-*N*-((*E*)-2-phenylcyclopropyl)-*N*-methylaniline (12). In an oven-dried 25-mL volume reaction flask equipped with a stirring bar, 1.4 g (9.98 mmol) of 4-chloro-*N*-methylaniline and 1.1 g (9.2 mmol) of freshly distilled phenylacetaldehyde were dissolved in 10 mL of dry benzene.[25] A condenser mounted on a Dean−Stark trap was affixed to the flask and the reaction was heated at reflux with stirring for approximately 3 h or until the formation of water was no longer noticeable as observed in the trap. Then a small aliquot was drawn with a syringe and the solvent was removed. The ^{1}H NMR of the remaining residue indicated the formation of the desired enamine and appeared to be very pure. The reaction mixture was cooled and the solvent was removed under pressure to give the product as a pale yellow solid. GC and GC−MS spectrometry showed that the enamine was more than 97% pure. The enamine was not purified any further and was used directly for the next reaction: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.31−7.23 (m, 7H), 7.13−7.07 (m, 1H), 6.98 (d, 2H, J = 9.0 Hz), 5.7 (d, 1H, J = 14 Hz), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 146.23, 138.53, 133.56, 129.23, 128.66, 126.34, 124.73, 124.44, 118.87, 104.62, 35.64; MS (70 eV): 245 ((M + 2)$^+$, 35), 244 ((M + 1)$^+$, 22), 243 ((M$^+$, 100), 242 (15), 207 (18), 107 (23), 106 (10), 105 (21), 11 (12), 91 (47), 88 (12), 77 (20), 75 (17), 65 (13), 51 (15).

The enamine was subjected to cyclopropanation by using a modification of the Simmons−Smith reaction.[26,27] In an oven-

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dried two-neck reaction flask equipped with a stirring bar and a rubber septa (at one neck) and an addition funnel (at the second neck), 4 g (16.4 mmol) of enamine **11** was dissolved in 30 mL of dry benzene. The solution was cooled to 0 °C, and 25 mL of diethyl zinc solution in hexane (2.53 g; 20.5 mmol of Et_2Zn) was added via a syringe under nitrogen. To the stirring mixture, 5.35 g (20.5 mmol) of diiodomethane (CH_2I_2) was added dropwise (by means of the addition funnel) under nitrogen atmosphere over a period of 30 min. The resulting dark yellow solution was gradually warmed to room temperature and then was allowed to further stir for 2 h. The reaction mixture was diluted with 50 mL of ether, transferred to a separatory funnel, and carefully washed twice with 45 mL of 10% aqueous NH_4OH solution, twice with 50 mL of water, and once with brine. All aqueous washes were back-extracted with 50 mL of ether. The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by distillation under reduced pressure to give a clear yellow oil in 69% yield (2.9 g): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.40−7.15 (m, 7H), 6.82 (d, 2H, J = 9.0 Hz), 3.05 (s, 3H), 2.64−2.58 (m, 1H), 2.14−2.07 (m, 1H), 1.40−1.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 148.86, 140.76, 128.68, 128.49, 126.06, 125.74, 122.49, 114.93, 44.00, 38.60, 27.42, 18.61. Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; N, 5.43. Found C, 74.57; H, 6.19; N, 5.52.

General Procedure for the Nitrosation of *N*-Cyclopropyl-*N*-alkylanilines. To a stirring solution of *N*-cyclopropyl-*N*-alkylaniline derivative in glacial acetic acid (3 mL of HOAc/mmol of substrate) at 0 °C was added dropwise $NaNO_2$ (2 mmol of $NaNO_2$/mmol of substrate) dissolved in H_2O (2 mL/mmol) via a syringe. Once the addition began, the reaction mixture became yellow and the intensity of the color increased with the progress of the reaction. The progress of the reaction was monitored by thin layer liquid chromatography. The reaction is usually complete within several minutes after the addition of $NaNO_2$. Once completed, the reaction mixture was carefully neutralized with a saturated aqueous solution of K_2CO_3 or Na_2CO_3. After neutralization, the resulting solution was extracted in diethyl ether (10 mL/mmol). The ether layer was washed three times with water and once with saturated aqueous solution of sodium chloride. The aqueous washes were back-extracted with ether. The two ether layers were combined and dried over anhydrous $MgSO_4$ or Na_2SO_4. The solvent was removed under reduced pressure on a rotary evaporator. The resulting residues were purified by flash column chromatography on silica gel (for a detailed example, see the nitrosation of 4-chloro-*N*-cyclopropyl-*N*-methylaniline, **10b**).

The Nitrosation of 4-Chloro-*N*-cyclopropyl-*N*-methylaniline (10b). In a reaction flask equipped with a stirring bar, 500 mg (2.75 mmol) of 4-chloro-*N*-cyclopropyl-*N*-methylaniline (**10b**) was dissolved in 6 mL of glacial acetic acid. The solution was cooled to 0 °C, and 380 mg (5.51 mmol) of $NaNO_2$ dissolved in 2 mL of H_2O was added dropwise over a period of 10 min while the reaction stirred. The resulting yellow solution was stirred at 0 °C for approximately 25 min. TLC showed reaction completion. Then, the reaction mixture was carefully neutralized (dropwise) with saturated aqueous Na_2CO_3 solution. The resulting mixture was diluted with 30 mL of ether and transferred to a separatory funnel. The aqueous layer was discarded and the remaining organic layer was washed once with saturated aqueous Na_2CO_3 solution (10 mL), 3 × 20 mL of H_2O, and once with brine. The aqueous washes were back-extracted with 30 mL of ether. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting reddish residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to give a yellow crystalline substance in 68% yield as the sole product (97% by HPLC analysis). Spectral data analysis indicated that the product is 4-chloro-*N*-methyl-*N*-nitrosoaniline[2] (**13b**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (dt, 2H, J = 2.4, 8.9 Hz), 7.45 (dt, 2H, J = 2.4, 8.9 Hz), 3.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.82, 132.88, 129.57, 120.10, 31.18.

4-Chloro-*N*-cyclopropyl-*N*-nitrosoaniline (17). The nitrosation of 4-chloro-*N*-cyclopropylaniline **10a** (65 mg, 0.39 mmol) under the same reaction conditions described in the general nitrosation procedure ($NaNO_2$, HOAc, H_2O, 0 °C, 15 min) followed by workup and chromatographic purification (eluted with 5% ethyl acetate in hexanes) gave the product as a yellow oil in 84% yield. The structure was confirmed by spectral data analysis: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53−7.47 (m, 2H), 7.43−7.40 (m, 2H), 2.92 (m, 1H), 1.21−1.10 (m, 2H), 0.58−0.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.84, 132.59, 129.21, 121.70, 26.70, 8.17; IR (neat) 1494s, 1487s, 1467s (sh) cm^{-1}. Anal. Calcd for $C_9H_9ClN_2O$: C, 54.93; H, 4.58; N, 14.24. Found C, 54.69; H, 4.44; N, 14.05.

The Nitrosation of 4-Chloro-*N*-cyclopropyl-*N*-ethylaniline (10c). The nitrosation of 280 mg (1.43 mmol) of 4-chloro-*N*-cyclopropyl-*N*-ethylaniline (**10c**) according to the general nitrosation procedure gave *N*-ethyl-*N*-nitroso-4-chloroaniline[1] (**13c**) in 66% yield (isolated yield) as a yellowish crystalline substance. No other nitrosation products were observed: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.50−7.41 (m, 4H), 4.04 (q, 2H, J = 7.15 Hz), 1.16 (t, 3H, J = 7.15 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 139.94, 132.85, 129.59, 120.45, 38.87, 11.59.

The Nitrosation of 4-Chloro-*N*-benzyl-*N*-cyclopropylaniline (10d). The nitrosation of 4-chloro-*N*-benzyl-*N*-cyclopropylaniline (**10d**) (350 mg, 1.36 mmol) and chromatographic purification (eluted with 10% ethyl acetate in hexanes) gave 4-chloro-*N*-benzyl-*N*-nitrosoaniline[1,28] (**13d**) as a yellow solid (mp 56 °C) in 69% yield (isolated): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.49−7.35 (m, 4H), 7.33−7.20 (m, 3H), 7.07−7.03 (m, 2H), 5.21 (s, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 140.28, 133.96, 132.97, 129.59, 128.91, 127.76, 126.97, 120.58, 46.93.

The Nitrosation of *N*-Cyclopropyl-*N*-isopropyl-4-chloroaniline (10f). The nitrosation of *N*-cyclopropyl-*N*-isopropyl-4-chloroaniline (**10f**) (175 mg, 0.83 mmol) followed by chromatographic purification on silica gel (eluted with 8% ethyl acetate in hexanes) gave *N*-isopropyl-*N*-nitroso-4-chloroaniline[29] (**13f**) as a yellow oil in 62% yield (isolated yield). The product was obtained as an inseparable mixture of two isomers in a ratio of 1.6:1: ^{1}H NMR ($CDCl_3$, 250 MHz; the spectral data for the isomeric mixture) δ 7.48 (m, includes two protons for each of the two isomers; 4H), 7.28 (dt, 2H, J = 2.8, 8.8 Hz; major isomer), 6.90 (dt, 2H, J = 2.0, 8.7 Hz; minor isomer), 1.53 (septet, 1H, J = 6.9 Hz; major isomer), 5.05 (septet, 1H, J = 6.8 Hz; minor isomer), 1.46 (d, 6H, J = 6.8 Hz; minor isomer), 1.18 (d, 6H, J = 6.9 Hz; major isomer); ^{13}C NMR ($CDCl_3$, 62.9 MHz; the spectral data for both isomers), δ 138.08, 135.28, 134.86, 134.68, 129.65, 129.32, 129.06, 127.00, 56.01, 46.23, 22.00, 19.69; IR (neat; both isomers) 1494s, 1448s cm^{-1}. Anal. Calcd for $C_9H_{11}ClN_2O$: C, 54.41; H, 5.58; N, 14.10. Found C, 54.23; H, 5.71; N, 13.93.

The Nitrosation of Ethyl 4-*N*-Cyclopropyl-*N*-methylaminobenzoate (10e). The nitrosation of ethyl 4-*N*-cyclopropyl-*N*-methylaminobenzoate **10e** (150 mg, 0.76 mmol) followed by chromatographic purification (eluted with 15% ethyl acetate in hexanes) resulted in ethyl 4-methylnitrosaminobenzoate[2] (**13e**) in 76% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (d, 2H, J = 8.8 Hz), 7.64 (d, 2H, J = 8.8 Hz), 4.41 (q, 2H, J = 7.2 Hz), 3.46 (s, 3H), 1.42 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.69, 145.52, 130.94, 128.82, 117.77, 61.16, 30.49, 14.27.

The Nitrosation of *N*-Cyclopropy-*N*-methylbenzylamine (20). The nitrosation of *N*-cyclopropy-*N*-methylbenzylamine (**20**) (70 mg, 0.43 mmol) according to the general nitrosation procedure ($NaNO_2$−H_2O/glacial HOAc) at room temperature followed by workedup in ether (usual aqueous workup as described in the general nitrosation procedure) and purification on silica gel (column chromatography; 10% ethyl acetate in hexanes) gave benzylmethylnitrosamine (**21**) as a yellow oil in 88% yield. The product was obtained as an inseparable mixture of *Z* and *E* isomers in a 3:1 ratio, and no other products were observed. The reaction was complete in about 55−65 min at room temperature. When the nitrosation

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was carried at 60 °C, it was completed in 15 min, giving similar results (86% yield in a 3:1 ratio). The spectral data were consistent with benzylmethylnitrosamine: ^{1}H NMR for the mixture ($CDCl_3$, 500 MHz) δ 7.40−7.30 (m, includes three protons for the major isomer and three protons for the minor isomer), 7.26 [(d, 2H (major isomer), J = 7.0 Hz)], 7.12 [(d, 2H (minor isomer), J = 7.0 Hz)], 5.29 (s, 2H, benzylic protons of the major isomer), 4.80 (s, 2H, benzylic proton of the minor isomer), 3.68 (s, 3H, methyl group of the minor isomer), 2.93 (s, 3H, methyl group of the major isomer); ^{13}C NMR for both isomers ($CDCl_3$, 125.8 MHz) δ 134.19, 133.65, 128.90, 128.74, 128.39, 128.19, 127.90, 127.80, 57.39, 47.57, 38.26, 30.56; IR (neat; both isomers) 1449s cm^{-1}; MS (70 eV) 150 (M^+, 16), 91 (100), 65 (13). Anal. Calcd for $C_8H_{10}N_2O$: C, 65.73; H, 6.89; N, 19.16. Found: C, 65.61; H, 6.88; N, 18.93.

The Nitrosation of 4-Chloro-*N*-(2-phenylcyclopropyl)-*N*-methylaniline (12). 4-chloro-*N*-(2-phenylcyclopropyl)-*N*-methylaniline **(12)** was nitrosated ($NaNO_2$−HOAc, 0 °C) according to the general nitrosation procedure described earlier. The reaction was complete in 15−20 min. Workup followed by chromatographic purification on silica gel (eluted with gradient: 2.5%, 3%, 5%, 15%, 15%, 20% and 25% ethyl acetate in hexanes) yielded 4-chloro-*N*-methyl-*N*-nitrosoaniline (**13b**) in 76%, cinnamaldehyde in 53%, compound **16** in 8%, and compound **15** in 26%.

Compound 16: 5-(*N*-4-chlorophenylmethylamino)-3-phenylisoxazoline. This product was obtained in 8% yield as a white solid substance (mp 191−192 °C) from the nitrosation of *N*-(2-phenylcyclopropyl)-*N*-methyl-4-chloroaniline (**12**): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.71−7.67 (m, 2H), 7.43−7.40 (m, 3H), 7.23 (d, 2H, J = 9.0 Hz), 6.98 (d, 2H, J = 9.0 Hz), 6.24 (dd, 1H, J = 4.8, 10.0 Hz), 3.51 (dd, 1H, J = 10.0, 17.8 Hz), 3.28 (dd, 1H, J = 4.8, 17.8 Hz), 2.78 (s, 3H); ^{13}C NMR (62.9 MHz) δ 155.34, 148.02, 130.17, 129.46, 129.09, 128.81, 126.52, 126.42, 119.78, 93.43, 37.01; IR (KBr pellet) 3075w, 3063w, 2958w, 2939w, 2921w, 2830w, 1593m, 1565w, 1487s, 1446m, 1432w, 1358s, 1312s, 1283w, 1255m, 1249m, 1193w, 1188m, 1112m, 1075w, 1007w, 976m, 930m, 914s, 887m, 832s, 802w, 758s, 749s, 692s, 672s, 656m, 537m, 520m cm^{-1}; MS (70 eV) 288 ($(M + 2)^+$, 10), 286 (M^+, 27), 187 (12), 186 (19), 143 (32), 142 (15), 141 (100), 140 (25), 118 (14), 77 (25), 51 (11). Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77. Found: C, 67.12; H, 5.10; N, 9.63.

Compound 15: 5-Hydroxy-3-phenylisoxazoline. This compound[6] was produced in 26% yield as a white solid substance (mp 117−118 °C) from the nitrosation reaction of *N*-(2-phenylcyclopropyl)-*N*-methyl-4-chloroaniline (**7**): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.70−7.61 (m, 2H), 7.43−7.33 (m, 3H), 6.03 (dd, 1H, J = 1.8, 6.5 Hz), 4.11 (br d, 1H, J = 2.3 Hz), 3.40 (dd, 1H, J = 6.5, 17.5 Hz), 3.23 (dd, 2H, J = 1.8, 17.5 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 156.87, 130.38, 128.96, 128.72, 126.91, 98.00, 42.45; IR (KBr bellet) 2944m, 2865w, 1599m, 1571m, 1499m, 1449s, 1404s, 1359s, 1333s, 1319w, 1294w, 1274s, 1243s, 1189w, 1181s, 1102w, 1084s, 1024w, 1000w, 931s, 905s, 974s, 841s, 800m, 761s, 689s, 672m, 552m, 515m cm^{-1}; MS (70 eV) 163 (M^+, 40), 135 (44), 134 (54), 119 (12), 117 (14), 106 (17), 103 (43), 91 (26), 89 (10), 78 (10), 77 (100), 64 (16), 63 (17), 51 (52). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.35; H, 5.37; N, 8.50.

Cyclopropylbenzylnitrosamine (19). Nitrosation of *N*-cyclopropylbenzylamine (**18**) (42 mg, 0.28 mmol) under the same reaction conditions discussed earlier ($NaNO_2$, HOAc, H_2O, 0 °C, 15−20 min) and chromatographic purification (12% ethyl acetate in hexanes) gave the product as a yellow oil in 86% yield. The product was obtained as an inseparable mixture of two geometric isomers in a ratio of 3.2:1. The product was identified by spectral data analysis: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.25 (m, includes 5H for the minor isomer and 3H for the major isomer), 7.16 (d, 2H, J = 7.0 Hz, major isomer), 5.25 (s, 2H, benzylic proton of the minor isomer), 4.80 (s, 2H, benzylic protons of the major isomer), 3.22 (m, 1H, the methine proton in the cyclopropane ring of the major isomer), 2.69 (m, 1H, the methine proton of the cyclopropane ring of the minor isomer), 1.17−1.03 (m, 2H, a methylene group protons of the cyclopropane ring in the major isomer), 1.01−0.92 (m, 2H, the second methylene group protons of the cyclopropane ring of the major isomer), 0.89−0.82 (m, 2H, a methylene group protons of the cyclopropane ring of the minor isomer), 0.68−0.59 (m, 2H, the second methylene group protons of the cyclopropane ring in the minor isomer); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.69, 134.40, 128.82, 128.66, 128.27, 128.15, 127.68, 127.55, 55.39, 48.70, 33.64, 27.37, 5,87, 5.74; IR (neat) 1496m, 1454s, 1443s, 1419m cm^{-1}; low resolution mass spectrometry gave a parent ion peak at 176: MS (70 eV) 146 (9), 133 (9), 91 (100), 65 (14). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.31; H, 6.78; N, 16.11.

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