Electrophilic Aromatic Substitution with *N*-Methoxy-*N*-acylnitrenium Ions Generated from *N*-Chloro-*N*-methoxyamides: Syntheses of Nitrogen Heterocyclic Compounds Bearing a *N*-Methoxyamide Group

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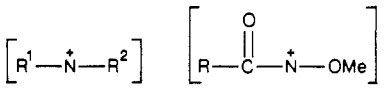
N-Methoxy-*N*-acylnitrenium ions (II), generated by treatment of *N*-chloro-*N*-methoxyamides with silver carbonate in trifluoroacetic acid, react with arenes to give *N*-aryl-*N*-methoxyamides in good yields. In the case of the intramolecular cyclization of *N*-chloro-*N*-methoxy-2-phenylacetamides, the mode of cyclization is highly dependent on the nature of ortho or para substituent groups. Nitrenium ions II can primarily attack three positions (C-1, C-2, and C-6) of a phenyl ring. Normally II attack C-6. On the other hand, when the ortho position was occupied with a substituent group, II attacked both C-2 and C-6, in the former case followed by a 1,2-substituent migration, which was proved by a deuterium labeling experiment. Especially, when a methoxy group is substituted on ortho or para position, II attack C-1 due to the effect of the electron-releasing methoxy group to give spiro dienone compounds **39**. A general discussion of the utility and mechanistic details of these reactions is presented.

Divalent positively charged nitrogen species which have been known as nitrenium ions (I)[1] have continued to be of great interest because of fundamental interest in their chemistry and possible synthetic utility and their importance as putative intermediates in the mechanism of action of several carcinogenic aromatic nitro and amino compounds.[2]



I II

Nitrenium ions (I) have been reported to be involved in the reactions of *N*-chloroamines,[3] *N*-chloroamides,[4] organic azides,[5,1c] hydroxylamines,[6] and hydrazines.[7]

In spite of the potenial utility of I as an electrophilic nitrogen, methods for generation of this cation to be introduced as a nitrogen functionality into aromatics have only recently surfaced, e.g., arylnitrenium ions generated by decomposition of arylazides in acidic media,[8] (ethoxycarbonyl)nitrenium ion generated by decomposition of ethyl azidoformate,[9] and nitrenium and alkylnitrenium ions generated by photolysis and thermolysis of 1-(amino and alkylamino)-2-(methyl and phenyl)-4,6-diphenylpyridinium tetrafluoroborates.[10] Since it is suggested by MNDO calculations that the singlet state of I is stabilized by the ability of the substituent group on the nitrogen atom to delocalize the positive charge and that the arylnitrenium and *N*-acetyl-*N*-arylnitrenium ions were stabilized by electron transfer from the phenyl substituent to the formally electron-deficient nitrogen atom,[11] acylnitrenium ions will be stabilized by an electron-donating group attached to a nitrogen atom.

Table I. Cyclization of 2 To Form 3 under Various Conditions

run	metal salt (equiv[a])	solvent	temp, °C; time, h	yield of 3,[b] %
1	$FeSO_4 \cdot 7H_2O$ (1)	c. H_2SO_4	0; 1.3	0[c]
2	$FeSO_4 \cdot 7H_2O$ (1)	TFA	−10; 1	2[d]
3	Ag_2SO_4 (2)	TFA	0; 1	82
4	Ag_2SO_4 (2)	MeOH	25; 24	0[e]
5	Ag_2SO_4 (2)	AcOH	25; 3.5	26[f]
6	Ag_2SO_4 (2)	80% H_2SO_4	0 → 25; 1.5	0[g]
7	Ag_2SO_4 (2)[h]	CH_2Cl_2	0; 1	0[i]
8	Ag_2SO_4 (2)	TFA	25; 0.5	39[j]
9	Ag_2SO_4 (1)	TFA	0; 1	77
10	Ag_2SO_4 (0.5)	TFA	0; 1	49
11	Ag_2CO_3 (2)	TFA	0; 0.5	87
12	AgOCOMe (3)	TFA	0; 0.5	67
13	$AgOSO_2CF_3$ (3)	TFA	0; 0.5	87
14	$AgOCOCF_3$ (3)	TFA	0; 0.5	75
15	$AgBF_4$ (3)	TFA	0; 0.3	70

[a] Molar equiv with respect to **2**. [b] Isolated yield. [c] Plus 43% of **1**. [d] Plus 55% of **1**. [e] Plus 66% of **2**. [f] Plus 11% of **2**. [g] Plus 55% of **1**. [h] Plus 1 equiv of $AlCl_3$. [i] Plus 91% of **1**. [j] Plus 16% of **1**.

We have preliminarily reported that *N*-methoxy-*N*-acylnitrenium ions (II) generated from *N*-chloro-*N*-methoxyamides by using a silver salt and trifluoroacetic acid (TFA) were convenient sources for the introduction of a methoxyamide group into arenes.[12] Ions II thus generated are stabilized by electron-releasing methoxy group and are long-lived enough to react with an aromatic ring.

We report here full details of our experiments on II and the new syntheses of nitrogen heterocyclic compounds bearing a *N*-methoxyamide group.

Results and Discussion

The first attempt to synthesize benzene-fused nitrogen heterocyclic compounds through the electrophilic intramolecular cyclization of aralkylhydroxylamines[13] revealed limited success;[14] in particular indoline derivatives could not be obtained at all. We have finally discovered that

(1) (a) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26. (b) Lansbury, P. *Nitrenes*; Lwowski, W., Ed.; Wiley-Interscience: New York, 1970; p 405. (c) Abramovitch, R. A.; Jeyaraman, R. *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic Press: New York, 1984; pp 297-357.

(2) Miller, J. A. *Cancer Res.* **1970**, *30*, 559 and references therein.

(3) Gassman, P. G.; Campbell, G. A.; Frederick, R. C. *J. Am. Chem. Soc.* **1972**, *94*, 3884. Gassman, P. G.; Campbell, G. A. *Ibid.* **1972**, *94*, 3891.

(4) Starewitz, P. M.; Sackett, A.; Kovacic, P. *J. Org. Chem.* **1978**, *43*, 739.

(5) Abramovitch, R. A.; Kyba, E. P. *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1971; pp 221-329.

(6) Gassman, P. G.; Hartman, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 449.

(7) Rosa, M. D.; Haberfield, P. *J. Org. Chem.* **1981**, *46*, 2639 and references therein.

(8) Zanirato, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1065. Spagnolo, P.; Zanirato, P. *Tetrahedron Lett.* **1987**, *28*, 961. Takeuchi, H.; Takano, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 611.

(9) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Chem. Commun.* **1982**, 226.

(10) Takeuchi, H. *J. Chem. Soc., Chem. Commun.* **1987**, 961. Abramovitch, R. A.; Evertz, K.; Huttner, G.; Gibson, H. H., Jr.; Weems, H. G. *Ibid.* **1988**, 325.

(11) Ford, G. P.; Scribner, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 4281.

(12) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728.

(13) Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 643.

(14) Kawase, M.; Kikugawa, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1615.

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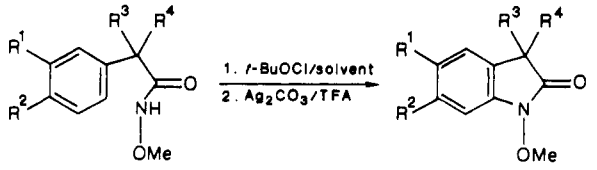
Table II. Synthesis of 1-Methoxy-2-oxindoles from *N*-Methoxyphenylacetamides

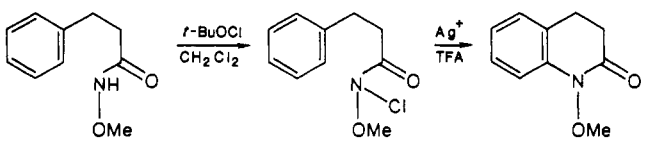


compd	R^1	R^2	R^3	R^4	solvent	product	yield,[a] %
8a	MeO	MeO	H	H	Et_2O	9a	73
8b	H	Cl	H	H	CH_2Cl_2	9b	87
8c	H	Br	H	H	CH_2Cl_2	9c	89
8d	H	Me	H	H	CH_2Cl_2	9d	82
8e	H	NHCOMe	H	H	Et_2O–CH_2Cl_2 (1:1)	9e	64
8f	H	NO_2	H	H	CH_2Cl_2	9f	32[b]
8g	H	MeO	Me	H	Et_2O–CH_2Cl_2 (1:1)	9g	96
8h	H	MeO	Me	Me	4% $Na_2B_4O_7$ in MeOH	9h	91
8i	H	MeO	NPhth[c]	H	CH_2Cl_2	9i	75

[a] Isolated yield of pure product from 8. [b] Plus 56% of 4-nitrophenylacetic acid. [c] *N*-Phthaloyl.

nitrenium ions derived from *N*-chloro-*N*-methoxyamides with silver salts in the presence of TFA exhibit strong electrophilic reactivity.

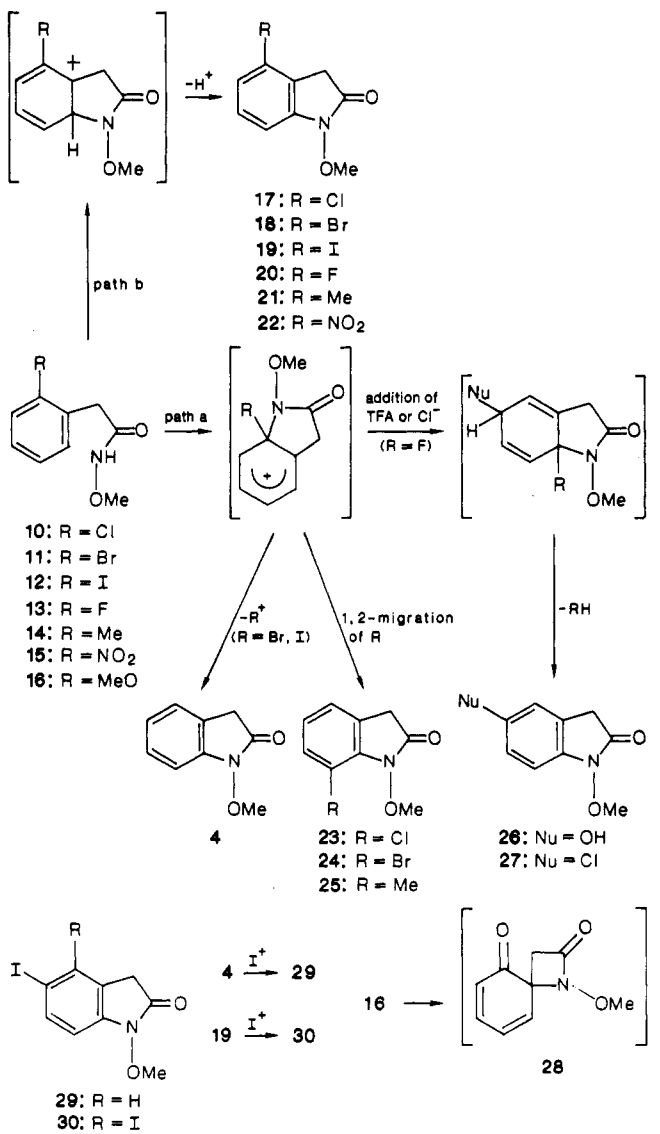
A. Intramolecular Aromatic Substitution. *N*-Chloro-*N*-methoxy-3-phenylpropionamide (**2**), synthesized in quantitative yield by chlorination of *N*-methoxy-3-phenylpropionamide (**1**) with *tert*-butyl hypochlorite in CH_2Cl_2, seems the ideal starting material for the determination of optimum conditions. Intramolecular cycli-



zation of **2** was attempted under various conditions. The results are summarized in Table I. As is shown in runs 6 and 7, a substantial amount of hydrogen-abstraction product **1** was recovered, which suggests that the mechanism changed from nitrenium ion to amino radical or that the rapid spin inversion from a singlet to a triplet nitrenium ion occurred.[1a] The radical mechanism is more plausible because similar results were obtained with the reaction of **2** and a radical generator[15] (runs 1 and 2). A combination of a silver ion and acidic media in which TFA usually gave best results was essential to generation of II and subsequent smooth cyclization.

Several *N*-chloro-*N*-methoxyamides were submitted to this cyclization reaction under the condition of run 11. The results are presented in Table II in which the following products previously reported[12] are omitted: 1-methoxy-2-oxindole (**4**) (93%); 3,4-dihydro-1-methoxycarbostyril (**3**) (87%); 1,3,4,5-tetrahydro-1-methoxy-1-benzazepin-2-one (**5**) (60%); 1,3-dihydro-1-methoxy-2*H*-benz[*e*]indol-2-one (**6**) (68%); 1,3-dihydro-1-methoxy-2*H*-benz[*c*]indol-2-one (**7**) (69%). Cyclization reaction proceeded smoothly in all the compounds except the *N*-chloride of **8f**, which was consistent with the fact that an electron-withdrawing substituent group retarded the aromatic substitution reaction (see below). Compound **8f** and *N,N'*-dimethoxy-*N,N'*-bis(4-nitrophenylacetyl)hydrazine derived from the dimerization of *N*-methoxy-*N*-acylamidyl[16] obtainable in radical cation mechanism were not isolated; instead, a

Scheme I



considerable amount of 4-nitrophenylacetic acid was isolated. In the case of the cyclization of *N*-chloro-*N*-methoxy-2-phenylacetamides (**10**–**16**) bearing ortho substituent groups, a nitrenium ion generated can primarily attack three positions of phenyl carbons (C-1, C-2, and C-6). Several ortho-substituted *N*-methoxy-2-phenylacetamides

(15) Minisci, F. *Synthesis* **1973**, 1.
(16) Forrester, A. R.; Johansson, E. M.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1112.

Table III. Cyclization of Ortho-Substituted N-Methoxyphenylacetamides

compd	cyclized product (yield, %)
10	17 (71), 23 (9)
11	18 (51), 24 (13), 4 (3)
12	19 (35), 29 (21), 4 (7), 30 (3)
13	20 (32), 26 (38), 27 (9), 4 (2)
14	21 (33), 25 (60)
15	22 (13)[a]

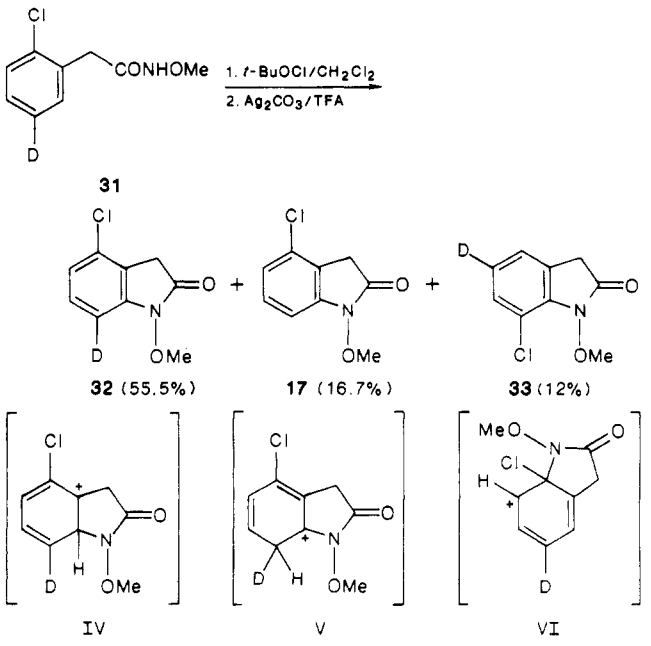
[a] Plus 54% of 2-nitrophenylacetic acid.

were submitted to the cyclization reaction. The results are presented in Scheme I and Table III.

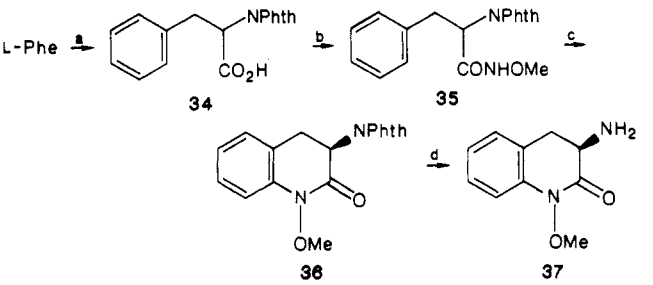
From *o*-methyl compound **14**, **25** was obtained in 60% yield in addition to **21** (33%) through the ipso intermediate (III, R = CH_3) formed by the attack of a nitrenium ion to C-2 and subsequent methyl migration to C-3. In the case of *o*-iodo compound **12**, 7-iodo-1-methoxy-2-oxindole was not detected by VPC; instead, **29** and **19** were obtained, which indicated the spontaneous decomposition of the intermediate (III, R = I) to **4** with the liberation of an iodonium cation and subsequent iodination to give **29**. In the case of *o*-fluoro compound **13**, a fluorine atom showed greater tenacity than other halogen atoms, and its migration products from III (R = F) were not detected at all; instead, III (R = F) was attacked by CF_3COO^- and Cl^- to give IV (Nu = $OCOCF_3$) and IV (Nu = Cl), which were aromatized with the loss of HF to give **26** and **27**, respectively. The reaction of *o*-methoxy compound **16** gave a complex mixture, in which the presence of 1-aza[3.5]-spirane (**28**) formed by the attack of a nitrenium ion to electron rich C-1 was suggested by the NMR data of the crude mixture (dienone H, multiplet, δ 6.10–7.00 ppm). The assumed **28** was less stable than other spiro compounds (vide post), and isolation and conversion to more stable derivatives were unsuccessful.

To confirm the assumed mechanism mentioned above, the mechanistic study was performed by a deuterium labeling experiment using 2-(2-chloro-5-deuteriophenyl)-*N*-methoxyacetamide (**31**); **31** was synthesized from 5-bromo-2-chlorobenzoic acid, which was deuterated on the C-5 position in 97.7% yield with Raney Cu–Al alloy[17] in 10% Na_2CO_3–D_2O solution followed by the Arndt–Eistert one carbon elongation method. Compound **31** was submitted to the cyclization reaction to give three compounds (**17**, **32**, and **33**) as shown in Scheme II. The presence of considerable amounts of deuterium free compound (**17**) (16.7%) coexisting with 7-deuterated compound (**32**) (55.3%) formed by the normal attack (C-6) with a nitrenium ion is interesting from a mechanistic viewpoint. The tertiary carbonium ion (IV) quenched by the loss of C-6 hydrogen gives **32**; this cation can shift to C-5 followed by a hydride shift from C-6 to C-5 to give V, which gives **17** and **32** by the loss of a deuterium atom and a hydrogen atom, respectively. On the other hand, the formation of **33** (12%) is explained by way of the ipso intermediate (VI) formed by the attack of a nitrenium ion at C-2 and the subsequent 1,2-shift of a chlorine atom to C-3, which confirms the assumed mechanism proposed previously[12] and excludes Glover's opinion.[18] Accordingly, other cases can be assumed as shown in Scheme I and Table III based upon the above results. Structural assignments of cyclization products were made on the basis of spectroscopic data (see the Experimental Section) and the transformations to the corresponding 2-oxindoles by reductive

Scheme II



Scheme III[a]



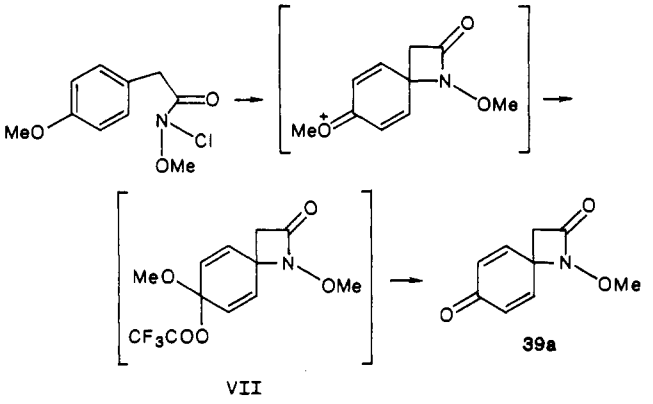
[a] (a) *N*-(Ethoxycarbonyl)phthalimide (87%); (b) $MeONH_2$·HCl/1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride/1-hydroxybenzotriazole/Et_3N/$ClCH_2CH_2Cl$ (74%); (c) (1) *t*-BuOCl/CH_2Cl_2, (2) Ag_2CO_3/TFA (94%); (d) NH_2NH_2·H_2O/EtOH (92%).

cleavage of the N–O bonds. This reaction proceeds without racemization. Optically active 3-amino-3,4-dihydrocarbostyril (**37**), which was synthesized from L-*o*-nitrophenylalanine[19] and showed antibacterial activities,[20] was readily synthesized from L-phenylalanine as shown in Scheme III.

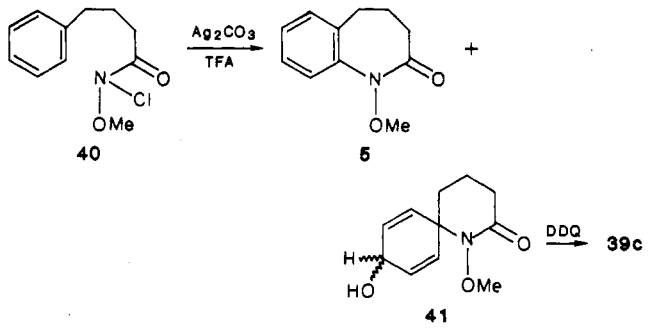
At the almost same time when we published a new methoxyamidation reaction,[12] Glover's group also succeeded the same kind of cyclization induced by nitrenium ions generated from *N*-alkoxy-*N*-chloroamides with silver tetrafluoroborate in benzene or methanol without acid.[21] Following their method by using *N*-chloro-*N*-methoxy-2-phenylacetamide from which 1-methoxy-2-oxindole (**4**) was obtained in 93% yield by our procedure, we have obtained **4** (15%) and *N*-methoxy-*N*-phenyl-2-phenylacetamide (32%) with silver tetrafluoroborate for 24 h in benzene, and methyl phenylacetate (92%) in methanol, respectively. Their method does not appear to be general from the synthetic point of view. It is evident that TFA plays an important role for the generalization of this reaction.

(17) Tashiro, M.; Iwasaki, A.; Fukata, G. *J. Org. Chem.* **1978**, *43*, 196.
(18) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577.
(19) Davis, A. L.; Smith, D. R.; Foyt, D. C.; Black, J. L.; McCord, T. J. *J. Med. Chem.* **1972**, *15*, 325.
(20) Davis, A. L.; Chambers, W. H.; Kelley, D. H.; Fell, D. A.; Haynes, J. R.; Hulme, K. L.; Gage, L. D.; McCord, T. J. *J. Med. Chem.* **1975**, *18*, 752.
(21) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2255.

Scheme IV



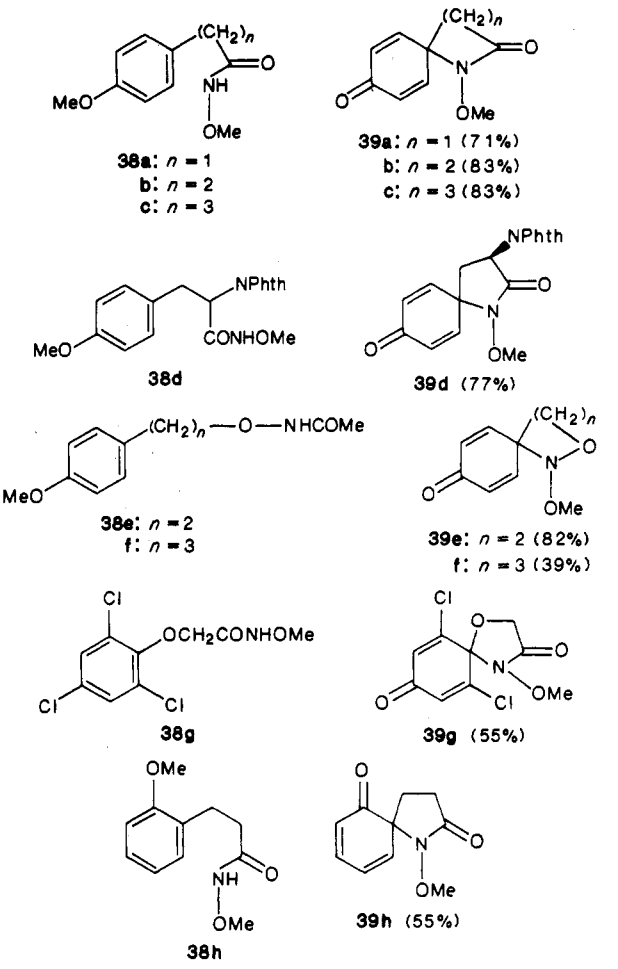
Scheme V



Recently we published[22] the same kind of an intramolecular cyclization reaction by using anhydrous zinc acetate and nitromethane as solvent in neutral conditions; however, more mechanistic studies are needed to determine the involvement of a nitrenium ion intermediate.

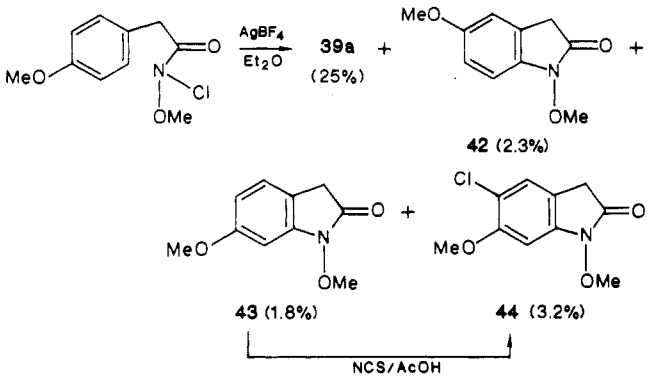
Syntheses of Spiro Lactams by Ipso Amidation with a Nitrenium Ion. Spiro lactams bearing the nitrogen atom bound to the spiro carbon were synthesized from *o*- or *p*-methoxybenzene derivatives by the intramolecular ipso attack with a nitrenium ion generated from the *N*-chloro-*N*-methoxyamide group in a molecule.[23] A nitrenium ion attacked the ipso position when the electron density of the position was increased by ortho or para substituent group. Several examples are listed in Chart I. The intermediate should be VII, which was hydrolyzed with the liberation[24] of methoxy group to give the spirodienone compound (Scheme IV). This mechanism is supported by the results of cyclization of *N*-chloro-*N*-methoxy-4-phenylbutyramide (**40**). As is shown in Scheme V, one of the products is **41**, which is formed by the attack with a nitrenium ion on the ipso position, and the positive charge carried in remains on the para position, to which the solvent (CF_3COOH) attacks before the proton departs. The NMR spectrum of **41** shows two singlets (δ 3.67, 3.72 ppm) of CH_3O and two broad singlets (δ 4.39, 4.57 ppm) of 9-H, which indicate the presence of two stereoisomers. The oxidation of **41** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane gave **39c** in 92% yield. Although several preparative methods[25] for the synthesis

Chart I



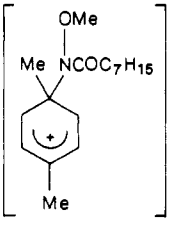
of spiro lactams have been reported, there has been no simple method having general applicability. According to this method reported herein, these spiro lactams were easily prepared and have a dienone moiety, which is modifiable by the usual chemical reactions, and may be supplied for the syntheses of functionalized spiro lactams. In the case of the reaction of (4-methoxyphenyl)-α-methyl-*N*-methoxyacetamide (**8g**), (4-methoxyphenyl)-α,α-dimethyl-*N*-methoxyacetamide (**8h**), and (4-methoxyphenyl)-α-phthalimido-*N*-methoxyacetamide (**8i**), the spirocyclization was prevented by the steric hindrance of α-substituent groups, and ortho amidation occurred instead to give the 1-methoxy-2-oxindoles **9g**, **9h**, and **9i** in the yields of 96%, 91%, and 75%, respectively. On the course of this investigation, we noticed that Glover's group published the synthesis of spiro lactams through the acylnitrenium ion intermediate, although the yields were generally not satisfactory.[18] For example, from *N*-chloro-*N*-methoxy-2-(4-methoxyphenyl)acetamide the spiro lactam **39a** was obtained in 9.9% yield by their method and 72% yield by our method. Moreover, following their experiment, we found that the compound they obtained and assumed to be chlorinated 1,5-dimethoxy-2-oxindole (**42**) (10.74%) was a mixture of 1,6-dimethoxy-2-oxindole (**43**) (1.8%) and 5-chloro-1,6-dimethoxy-2-oxindole (**44**) (3.2%), which was identified by the mixed melting point test with the authentic sample prepared by the chlorination[26] of 1,6-dimethoxy-2-oxindole (see Experimental Section).[22] As the yield of 6-methoxy compounds is proved to be better than that of 5-methoxy

(22) Kikugawa, Y.; Shimada, M. *Chem. Lett.* **1987**, 1771.
(23) Kawase, M.; Kitamura, T.; Kikugawa, Y. Presented in part at the 17th Congress of Heterocyclic Chemistry, Sapporo, Japan, August 1985. Abstracts of Papers, p 213.
(24) Barnett, J. W.; Moodie, R. B.; Schofield, K.; Weston, J. B.; Coombes, R. G.; Golding, J. G.; Tobin, G. D. *J. Chem. Soc., Perkin Trans. 2* **1977**, 248.
(25) Duhamel, L.; Poirier, J.-M.; Granger, P. *J. Org. Chem.* **1979**, *44*, 3576. Holmes, A. B.; Russell, K.; Stern, E. S.; Stubbs, M. E.; Wellard, N. K. *Tetrahedron Lett.* **1984**, *25*, 4163.
(26) Wright, W. B., Jr.; Collins, K. H. *J. Am. Chem. Soc.* **1956**, *78*, 221.



compound **42** (2.3%), Glover's conclusion that carbon migrates in preference to nitrogen becomes doubtful. The results of preferential migration tendency of alkoxyamide group in the dienone–phenol rearrangement will be published.[27]

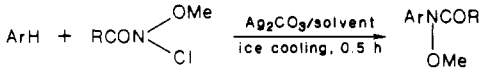
B. Intermolecular Aromatic Substitution. Ions II generated as described above react intermolecularly with arenes to give *N*-aryl-*N*-methoxyamides in good yield when a 5- or 10-fold excess of arenes to *N*-chloro-*N*-methoxyamides was used. Several arenes were submitted to this reaction. The results are presented in Table IV. Electron-releasing substituent groups of arenes facilitated the reaction, while electron-withdrawing substituent groups retarded the reaction. Thus, the reaction of methyl benzoate with **46a** (Chart II) proceeded in poor yield, and the following arenes did not react with **46a**: benzonitrile, *N*,*N*-dimethylbenzamide, pyridine, pyridine *N*-oxide, and quinoline. In the case of arenes bearing strong electron-releasing substituent groups, chlorination of aromatic ring occurred exclusively in TFA. To lower the acidity of solvent by using cosolvent (CH_2Cl_2, sulfolane, MeCN, DMF, and $MeNO_2$) in which $MeNO_2$ was found to be the most effective, the orientation of the reaction was changed from chlorination to *N*-methoxyamidation. The desired products were obtained in high yield in the 1:1–1:4 mixture of TFA and $MeNO_2$. From the reaction with *p*-xylene, **49a** was obtained in 71% yield concomitantly with the unexpected **49b** (4%), the formation of which could be rationalized by way of an ipso intermediate (VIII) and the subsequent methyl migration.



VIII

C. Mechanistic Consideration. Mechanistic studies involved electron-deficient nitrogen species are sometimes confusing because it is not easy to conclude clearly that the reaction is induced by nitrenium ions or nitrogen radicals. Nitrenium ions have been proposed as intermediates in the reaction of *N*-chloroamines[3,28] and *N*-chloroamides,[4] while amidyl radicals have also been suggested as possible intermediates in these reactions.[29,30]

Table IV. Intermolecular Reaction of Arenes with *N*-Chloro-*N*-methoxyamides



46

ArH (ArH/46 molar ratio)	46	solvent	product (yield, %)[a]
benzene (1)	a	TFA	**47a** (22)
benzene (3)	a	TFA	**47a** (62)
benzene (10)	a	TFA	**47a** (93)
benzene (10)	b	TFA	**47b** (71)
benzene (10)	c	TFA	**47c** (88)
benzene (10)	d	TFA–$MeNO_2$ (1:5)	**47d** (51)
toluene (5)	a	TFA	**48a–c** (85)[b]
p-xylene (5)	a	TFA	**49a** (75)[c]
anisole (5)	a	TFA–$MeNO_2$ (1:4)	**50a** (50) + **50b** (30)
naphthalene (5)	a	TFA–$MeNO_2$ (1:1)	**51a** (80) + **51b** (11)
methyl benzoate (5)	a	TFA	**52** (20)[b,d]

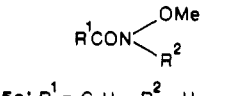
[a] Isolated yields based on **46** used. [b] A mixture of ortho, meta, and para isomers. [c] Compound **49b** was contained in 4%. [d] Isomer ratio was not determined.

Table V. Cyclization of 2 To Form 3

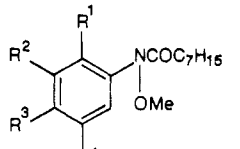
reaction conditions[a]	reaction time, [b] h	yield of 3,[c] %
under N_2	1	82
under O_2	1	76
DPPH (0.1 molar equiv[d])	1	78

[a] All the experiments were performed by using Ag_2SO_4 (2 molar equiv) in TFA at 0 °C. [b] Time required for complete consumption of **2**. [c] Isolated yield of pure **3**. [d] Molar equiv with respect to **2**.

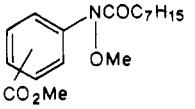
Chart II



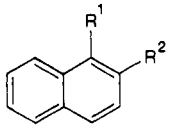
45a: $R^1 = C_7H_{15}$; $R^2 = H$
b: $R^1 = C_6H_5$; $R^2 = H$
c: $R^1 = C_6H_5CH_2O$; $R^2 = H$
d: $R^1 = t$-BuO; $R^2 = H$
46a: $R^1 = C_7H_{15}$; $R^2 = Cl$
b: $R^1 = C_6H_5$; $R^2 = Cl$
c: $R^1 = C_6H_5CH_2O$; $R^2 = Cl$
d: $R^1 = t$-BuO; $R^2 = Cl$
47a: $R^1 = C_7H_{15}$; $R^2 = C_6H_5$
b: $R^1 = R^2 = C_6H_5$
c: $R^1 = C_6H_5CH_2O$; $R^2 = C_6H_5$
d: $R^1 = t$-BuO; $R^2 = C_6H_5$



48a: $R^1 = Me$; $R^2 = R^3 = R^4 = H$
b: $R^1 = R^3 = R^4 = H$; $R^2 = Me$
c: $R^1 = R^2 = R^4 = H$; $R^3 = Me$
49a: $R^1 = R^4 = Me$; $R^2 = R^3 = H$
b: $R^1 = R^3 = Me$, $R^2 = R^4 = H$
50a: $R^1 = MeO$; $R^2 = R^3 = R^4 = H$
b: $R^1 = R^2 = R^4 = H$; $R^3 = MeO$



52



51a: $R^1 = N(OMe)COC_7H_{15}$; $R^2 = H$
b: $R^1 = H$; $R^2 = N(OMe)COC_7H_{15}$

In our case, radical mechanisms are not supported because an oxygen atmosphere or an addition of a radical scavenger *N*,*N*-diphenylpicrylhydrazil (DPPH)[31] did not affect the methoxyamidation reaction as shown in Table V. Furthermore, the presence of diacyldimethoxyhydrazines derived from the dimerization of *N*-methoxy-*N*-acylamidyls[16] or the corresponding methyl esters given

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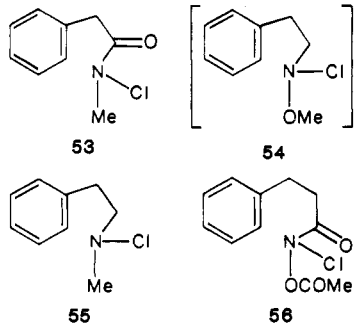
by the decomposition of the hydrazines[32] were not detected in the reaction mixtures.

The nitrenium ion formation is initiated by the silver cation, which induces heterolysis of the nitrogen–chlorine bond. Bearing no α-hydrogens, ions II thus formed are prevented from further reaction to *O*-methyloximes through dehydrochlorination and are stabilized by the adjacent electron-releasing methoxy group. On the other hand, all the analogues **53–56** failed to cyclize under the



same reaction conditions, and **54** was dehydrochlorinated to give the corresponding oxime. Acid is also the important factor for the success of this reaction, and TFA having the strong acidity and the low nucleophilicity of the trifluoroacetate anion was the best. However, in the case of the electron-rich arenes such as anisole and naphthalene, the electrophilic aromatic chlorination with **46a** was the competitive side reaction catalyzed by TFA. The rate of chlorination was retarded by diluting TFA with CH_3NO_2, and methoxyamidation of arenes prevailed.

In conclusion, it is evident from above-mentioned facts that singlet acylnitrenium ions are generated and undergo electrophilic aromatic substitution reactions.

Experimental Section

General Methods. All the melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^1H NMR spectra were measured on either a JEOL JNM-PMX60SI or a JEOL JNM-FX270 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent unless otherwise noted. ^{13}C NMR spectra were obtained on a JEOL JNM-FX270 spectometer (at 67.8 MHz). Both ^1H and ^{13}C NMR spectral data are reported in parts per million (δ) relative to Me_4Si. Infrared (IR) spectra were recorded on a JASCO IR810 spectrometer. Low- and high-resolution mass (MS) spectra were obtained with a JEOL JMS-DX300 spectrometer with a direct inlet system at 70 eV. Optical rotations were measured with a JASCO DIP-181 polarimeter. VPC analyses were performed on a Shimadzu GC-4BM instrument with either column A (2 m × 4 mm i.d.), packed with 10% SE-30 on 60–80 mesh Chromosorb W, or column B (25 m × 0.25 mm i.d.), packed with Poly-1-110. Combusion analyses were carried out in the microanalytical laboratory of this university. Where analyses are indicated by symbols of the elements, analytical results obtained for these elements were within ±0.3% of the theoretical value.

Materials. The following compounds were prepared by reported procedures: 2-iodophenylacetic acid,[32] 2,4,6-trichlorophenoxyacetic acid,[33] 2-(4-methoxyphenyl)propionic acid,[34] 2-(4-methoxyphenyl)-2-methylpropionic acid,[35] and **45b**.[36] *N*-[2-(4-Methoxyphenyl)ethoxy]acetamide (**38e**) was prepared from 1-bromo-2-(4-methoxyphenyl)ethane[37] and potassium acetohydroxamate[38] by the reported method:[21] yield, 67%; mp 82–83 °C (benzene). Anal. ($C_{11}H_{15}NO_3$) C, H, N. *N*-[3-(4-Methoxyphenyl)-1-propoxy]acetamide (**38f**) was prepared from 1-bromo-3-(4-methoxyphenyl)propane[18] and potassium acetohydroxamate[38] by the reported method:[21] yield, 65%; a colorless oil; MS calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1204. The following octanamides were prepared in high yield by Schotten–Baumann reactions of the appropriate aniline derivatives and octanoyl chloride. *N*-(2-Methylphenyl)octanamide: mp 67 °C (lit.[39] mp 69 °C). *N*-(3-Methylphenyl)octanamide: bp 240 °C (3 mmHg) (bath temperature); MS calcd for $C_{15}H_{23}NO$ 233.1780, found 233.1797. *N*-(4-Methylphenyl)octanamide: mp 66–67 °C (lit.[40] mp 67 °C). *N*-(2,5-Dimethylphenyl)octanamide: mp 100–104.5 °C (acetone–hexane). Anal. ($C_{16}H_{25}NO$) C, H, N. *N*-(2,4-Dimethylphenyl)octanamide: mp 90–91 °C (acetone–hexane). Anal. ($C_{16}H_{25}NO$) C, H. N. *N*-(2-Methoxyphenyl)octanamide: mp 47–48 °C (ligroin); MS calcd for $C_{15}H_{23}NO_2$ 249.1729, found 249.1743. *N*-(4-Methoxyphenyl)octanamide: mp 96–97 °C (benzene); MS calcd for $C_{15}H_{23}NO_2$ 249.1729, found 249.1725. *N*-(1-Naphthyl)octanamide: mp 98 °C (lit.[40] mp 95 °C). *N*-(2-Naphthyl)octanamide: mp 100–101 °C (lit.[40] mp 103 °C).

Phenylacetaldehyde *O*-methyloxime was prepared from phenylacetaldehyde and methoxyamine hydrochloride in 61% yield: a colorless oil; bp 84 °C (7 mmHg); MS calcd for $C_9H_{11}NO$ 149.0840, found 149.0819. *N*-Methoxyphenethylamine was prepared by the pyridine–borane reduction[13] of phenylacetaldehyde *O*-methyloxime in 81% yield: a colorless oil; ^1H NMR (60 MHz) δ 2.63–3.33 (m, 4 H), 3.55 (s, 3 H), 5.55 (br s, 1 H), 7.22 (s, 5 H); IR (neat) 3300 cm^{-1}; MS *m/e* 151 (M^+).

The following phthaloyl amino acids were prepared by the reported method.[41] **34**: yield, 87%; mp 185–186.5 °C (H_2O); $[\alpha]^{23}_D$ −223° (*c* 1, EtOH). *N*-Phthaloyl-DL-(4-methoxyphenyl)glycine: yield, 90%; mp 145–148 °C (H_2O). *N*-Phthaloyl-L-4-methoxyphenylalanine: yield, 81%; mp 64–66 °C (H_2O); $[\alpha]^{28}_D$ −190.2° (*c* 1, EtOH).

General Procedure for the Preparation of *N*-Methoxyamides. Method A. An acid chloride (50 mmol), prepared from the corresponding carboxylic acid and thionyl chloride, was added to a vigorously stirred solution of methoxyamine hydrochloride (55 mmol) and sodium carbonate (100 mmol) in a mixture of benzene (50 mL) and H_2O (50 mL) with cooling. The reaction mixture was stirred for 5 h at room temperature and then extracted with AcOEt (2 × 100 mL). The combined extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the *N*-methoxyamide, which was purified by column chromatography (SiO_2, benzene–AcOEt), recrystallization, or distillation. **1**: yield, 94%; bp 150–152 °C (2 mmHg). Anal. ($C_{10}H_{13}NO_2$) C, H, N. ***N*-Methoxy-2-phenylacetamide**: yield, 98%; mp 69–71.5 °C (lit.[18] mp 69–71 °C). ***N*-Methoxy-4-phenylbutyramide**: yield, 80%; mp 57.5–58 °C (lit.[18] mp 58.5–60.5 °C). ***N*-Methoxy-2-(1-naphthyl)acetamide**: yield, 94%; mp 106–107 °C ($CHCl_3$–hexane). Anal. ($C_{13}H_{13}NO_2$) C, H, N. ***N*-Methoxy-2-(2-naphthyl)acetamide**: yield, 92%; mp 139–140 °C ($CHCl_3$). Anal. ($C_{13}H_{13}NO_2$) C, H, N. **8b**: yield, 90%; mp 106–107 °C (AcOEt–hexane). Anal. ($C_9H_{10}ClNO_2$) C, H, N. **8c**: yield, 73%; mp 126.5–128 °C ($CHCl_3$). Anal. ($C_9H_{10}BrNO_2$) C, H, N. **8d**: yield, 91%; mp 91.5–92 °C ($CHCl_3$–hexane). Anal. ($C_{10}H_{13}NO_2$) C, H, N. **8f**: yield, 67%; mp 145.5–146.5 °C (AcOEt). Anal. ($C_9H_{10}N_2O_4$) C, H, N. **8g**: yield, 81%; mp 118–119 °C (AcOEt–hexane). Anal. ($C_{11}H_{15}NO_3$) C, H, N. **8h**: yield, 86%; a colorless oil; MS calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1208. **10**: yield, 94%; mp 113–114 °C ($CHCl_3$–hexane). Anal. ($C_9H_{10}ClNO_2$) C, H, N. **11**: yield, 72%; mp 112.5–114 °C ($CHCl_3$–hexane). Anal. ($C_9H_{10}BrNO_2$) C, H, N. **12**: yield, 98%; mp 136–137 °C ($CHCl_3$–hexane). Anal. ($C_9H_{10}INO_2$) C, H, N. **13**: yield, 98%; mp 82–82.5 °C ($CHCl_3$–hexane). Anal. ($C_9H_{10}FNO_2$) C, H, N. **14**: yield, 91%; mp 80–81.5 °C ($CHCl_3$–hexane). Anal. ($C_{10}H_{13}NO_2$) C, H, N. **15**: yield, 91%; mp 151–152 °C ($CHCl_3$). Anal. ($C_9H_{10}N_2O_4$) C, H,

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N. **16**: yield, 86%; mp 73–74 °C [$CHCl_3$-(*i*-Pr)$_2$O]. Anal. ($C_{10}H_{13}NO_3$) C, H, N. **38a**: yield, 98%; mp 87.5–88.5 °C (lit.[18] mp 83–85 °C). **38b**: yield, 91%; mp 72–73 °C (lit.[17] mp 70–71 °C). **38c**: yield, 80%; mp 53–54 °C [$CHCl_3$-(*i*-Pr)$_2$O] (lit.[18] mp 45 °C). Anal. ($C_{12}H_{17}NO_3$) C, H, N. **38g**: yield, 67%; mp 138–139 °C (bezene–hexane). Anal. ($C_9H_8Cl_3NO_3$) C, H, N. **38h**: yield, 82%; mp 90–91.5 °C (benzene). Anal. ($C_{11}H_{15}NO_3$) C, H, N. **45a**: yield, 82%; bp 132–134 °C (4 mmHg); MS calcd for $C_9H_{19}NO_2$ 173.1416, found 173.1404. **45c**: yield, 98%; bp 170 °C (2 mmHg) (bath temperature). Anal. ($C_9H_{11}NO_3$) C, H, N.

Method B. A mixture of a carboxylic acid (50 mmol), methoxyamine hydrochloride (55 mmol), triethylamine (55 mmol), and 1,3-dicyclohexylcarbodiimide (52.5 mmol) in CH_2Cl_2 (150 mL) was stirred for 16 h at room temperature. Acetic acid (1 mL) was then added to this solution, and the mixture was stirred for 0.5 h at room temperature. The precipitates were removed by filtration and washed with CH_2Cl_2. The combined filtrates were washed successively with 3% HCl (100 mL), H_2O (100 mL), 5% $NaHCO_3$ (100 mL), and H_2O (100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, benzene–AcOEt) or recrystallization. **8a**: yield, 80%; mp 112–113 °C ($CHCl_3$–hexane). Anal. ($C_{11}H_{15}NO_4$) C, H, N. **8i**: yield, 86%; mp 114–116 °C (AcOEt–hexane). Anal. ($C_{18}H_{16}N_2O_5$) C, H, N. **38d**: yield, 94%; mp 116–118 °C (AcOEt–hexane); $[\alpha]^{23}_D$ −138.0° (*c* 1, $CHCl_3$). Anal. ($C_{19}H_{18}N_2O_5$) C, H, N.

***N*-Methoxy-3-phenyl-2-phthalimidopropionamide (35).** A mixture of **34** (983 mg, 3.3 mmol), methoxyamine hydrochloride (334 mg, 3.9 mmol), Na_2CO_3 (194 mg, 1.8 mmol), and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (592 mg, 3.3 mmol) in $ClCH_2CH_2Cl$ (20 mL)–H_2O (4 mL) was stirred for 6 h at room temperature. The mixture was diluted with CH_2Cl_2 (30 mL) and H_2O (20 mL). The organic layer was separated and washed successively with 5% HCl (20 mL), H_2O (20 mL), 5% $NaHCO_3$ (20 mL), and H_2O (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel with AcOEt–hexane (2:1) as the eluent to give **35** (799 mg, 74%) as a colorless oil: $[\alpha]^{23}_D$ −114.0° (*c* 1, $CHCl_3$); MS calcd for $C_{18}H_{16}N_2O_4$ 324.1108, found 324.1080.

2-(4-Acetamidophenyl)-*N*-methoxyacetamide (8e). Compound **8d** (1 g, 4.76 mmol) in acetic anhydride (5 mL)–AcOEt (5 mL) containing 100 mg of 10% Pd–C was hydrogenated for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was basified with 5% Na_2CO_3 with cooling, and the precipitated solid **8e** was collected by filtration, washed with H_2O, and dried: yield, 70%; mp 180–182 °C (AcOEt). Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

***tert*-Butyl *N*-Methoxycarbamate (45d).** This was prepared from *tert*-butoxycarbonyl anhydride, methoxyamine hydrochloride, and sodium carbonate in a mixture of CH_2Cl_2 and H_2O and was purified by column chromatography on silica gel, eluting with benzene–AcOEt, (20:1) and used in the next reaction without further purification: yield, 72%; a colorless oil; ^1H NMR (60 MHz) δ 1.46 (s, 9 H), 3.65 (s, 3 H), 7.55 (br, 1 H); IR (neat) 1720, 3280 cm^{-1}; MS *m/e* 147 (M^+).

General Procedure for the Preparation of *N*-Chloro-*N*-methoxyamides. To a stirred solution of a *N*-methoxyamide (2 mmol) in CH_2Cl_2 (8 mL) was added slowly *tert*-butyl hypochlorite (2.4 mmol) with cooling. The reaction mixture was stirred at 0 °C in the dark until the reaction was complete (the time required was generally less than 20 min). The solvent was evaporated at 35 °C under reduced pressure, and the residue was chromatographed on a column of silica gel with AcOEt–benzene as the eluent to give a pure *N*-chloro-*N*-methoxyamide as a yellow oil. **2**: yield, 95%. The spectra match literature data.[18] ***N*-Chloro-*N*-methoxy-2-phenylacetamide**: yield, 98%. The spectra match literature data.[18] **40**: yield, 94%. The spectra match literature data.[18] ***N*-Chloro-*N*-methoxy-2-(1-naphthyl)acetamide**: yield, 92%. ***N*-Chloro-*N*-methoxy-2-(2-naphthyl)acetamide**: yield, 95%. ***N*-Chloro-2-(4-chlorophenyl)-*N*-methoxyacetamide**: yield, 93%. **2-(4-Bromophenyl)-*N*-chloro-*N*-methoxyacetamide**: yield, 95%. ***N*-Chloro-*N*-methoxy-2-(4-methylphenyl)acetamide**: yield, 95%. ***N*-Chloro-2-(2-chlorophenyl)-*N*-methoxyacetamide**: yield, 97%. **2-(2-Bromophenyl)-*N*-chloro-*N*-methoxyacetamide**: yield, 94%. ***N*-Chloro-2-(2-iodophenyl)-*N*-methoxyacetamide**: yield, 94%. ***N*-Chloro-2-(2-fluorophenyl)-*N*-methoxyacetamide**: yield, 99%. ***N*-Chloro-*N*-methoxy-2-(2-methylphenyl)acetamide**: yield, 95%. ***N*-Chloro-*N*-methoxy-2-(2-nitrophenyl)acetamide**: yield, 95%. **46a**: yield, 98%. **46b**: yield, 90%. The spectra match literature data.[18] *N*-Chlorinated **8f**, **8i**, **35**, **38d**, **38g**, **45c**, and **45d** were used in the next reaction without further purification. Compounds **8a**, **16**, **38a**, **38b**, **38c**, **38f**, and **38h** were N-chlorinated in Et_2O and **8e**, **8g**, and **38e** in Et_2O and CH_2Cl_2 (1:1), and they were used in the next reaction without further purification.

***N*-Chlorination of 8h.** To a stirred solution of **8h** (245 mg, 1.1 mmol) in 3 mL of 4% sodium borate in MeOH was added slowly *tert*-butyl hypochlorite (0.16 mL, 1.4 mmol) with cooling. The reaction mixture was stirred at 0 °C in the dark for 20 min. The mixture was diluted with Et_2O (60 mL) and brine (15 mL). The Et_2O layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to give *N*-chloro-*N*-methoxy-2-(4-methoxyphenyl)-2-methylpropionamide (191 mg, 67%) as a syrup. This material was used for the next reaction without further purification.

***N*-Chloro-*N*-methyl-2-phenylacetamide (53).** This was obtained from *N*-methyl-2-phenylacetamide[42] by the same method as described above and purified by column chromatography on silica gel eluting with benzene–AcOEt (20:1): yield, 75%; a yellow oil; ^1H NMR (60 MHz) δ 3.32 (s, 3 H), 3.83 (s, 2 H), 7.28 (s, 5 H); IR (neat) 1670 cm^{-1}.

***N*-Chloro-*N*-methylphenethylamine (55).** To a stirred solution of *N*-methylphenethylamine[43] (295 mg, 2.2 mmol) in Et_2O (5 mL) was added slowly *tert*-butyl hypochlorite (0.3 mL, 2.6 mmol) with cooling. The reaction mixture was stirred at 0 °C in the dark for 15 min. The mixture was diluted with Et_2O (30 mL) and H_2O (15 mL). The Et_2O layer was separated, washed with 1% H_2SO_4 (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel with benzene as the eluent to give **55** (274 mg, 74%) as a yellow oil: ^1H NMR (60 MHz) δ 2.97–3.07 (m, 4 H), 3.00 (s, 3 H), 7.27 (s, 5 H).

***N*-Acetoxy-*N*-chloro-3-phenylpropionamide (56).** To a stirred solution of *N*-acetoxy-3-phenylpropionamide[44] (297 mg, 1.4 mmol) and K_2CO_3 (3 mg) in a mixture of CCl_4 (3 mL) and $CHCl_3$ (1 mL) was added *tert*-butyl hypochlorite (0.2 mL, 1.8 mmol) with cooling. The reaction mixture was stirred at room temperature in the dark for 0.5 h. The solvent was evaporated at 35 °C under reduced pressure, and the residue was chromatographed on a column of silica gel with benzene–AcOEt (50:1) as the eluent to give **56** (257 mg, 75%) as a yellow oil: ^1H NMR (60 MHz) δ 2.17 (s, 3 H), 2.57–3.22 (m, 4 H), 7.23 (s, 5 H); IR (neat) 1740, 1810 cm^{-1}.

Attempted N-Chlorination of *N*-Methoxyphenethylamine. To a stirred solution of *N*-methoxyphenethylamine (175.4 mg, 1.16 mmol) in MeOH (3 mL) was added slowly *tert*-butyl hypochloride (0.14 mL, 1.24 mmol) with cooling. The reaction mixture was stirred at 0 °C in the dark for 5 min. The mixture was diluted with CH_2Cl_2 (50 mL) and brine (15 mL). The CH_2Cl_2 layer was separated, washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. First elution with benzene–hexane (1:1) afforded phenylacetaldehyde *O*-methyloxime (90.2 mg, 52%), which was identified by comparison of the spectral data with those of the authentic sample. Second elution with benzene–acetone (10:1) afforded the starting material (28.8 mg, 16%).

General Procedure for the Cyclization of *N*-Chloro-*N*-methoxyamides. A solution of silver carbonate (1.1 g, 4 mmol) in TFA (8 mL) was added to a *N*-chloro-*N*-methoxyamide (2 mmol) cooled in an ice bath with stirring. The stirring was continued for 15–30 min to complete the reaction, and then the solvent was removed under reduced pressure below 35 °C. The residue was basified with 5% Na_2CO_3 (20 mL) with cooling, the precipitated salts were filtered off, and the filter cake was washed with CH_2Cl_2. The aqueous solution was extracted with CH_2Cl_2

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(2 × 40 mL). The combined CH_2Cl_2 solution was washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with benzene–AcOEt to give the cyclized product. **3**: yield, 87%; bp 120–122 °C (1 mmHg). Anal. ($C_{10}H_{11}NO_2$) C, H, N. **4**: yield, 93%; mp 84–84.5 °C (lit.[26] mp 84–86 °C). **6**: yield, 68%; mp 111–111.5 °C (Et_2O). Anal. ($C_{13}H_{11}NO_2$) C, H, N. **7**: yield, 69%; mp 103.5–104.5 °C (Et_2O). Anal. ($C_{13}H_{11}NO_2$) C, H, N. **9a**: mp 114–116 °C (Et_2O). Anal. ($C_{11}H_{13}NO_4$) C, H, N. **9b**: mp 116–117 °C (Et_2O). Anal. ($C_9H_8ClNO_2$) C, H, N. **9c**: mp 119.5–120.5 °C (Et_2O). Anal. ($C_9H_8BrNO_2$) C, H, N. **9d**: mp 64–64.5 °C (Et_2O–hexane). Anal. ($C_{10}H_{11}NO_2$) C, H, N. **9e**: mp 204–206 °C (AcOEt). Anal. ($C_{11}H_{12}N_2O_3$) C, H, N. **9f**: mp 188–189 °C (AcOEt). Anal. ($C_9H_8N_2O_4$) C, H, N. **9g**: mp 63–64 °C (Et_2O). Anal. ($C_{11}H_{13}NO_3$) C, H, N. **9h**: bp 150 °C (2 mmHg) (bath temperature); mp 68–71 °C; MS calcd for $C_{12}H_{15}NO_3$ 221.1051, found 221.1052. **9i**: mp 156–158 °C (CH_2Cl_2–hexane). Anal. ($C_{18}H_{14}N_2O_5$) C, H, N. **17**: mp 77–78 °C (Et_2O–hexane). Anal. ($C_9H_8ClNO_2$) C, H, N. **18**: mp 104.5–105.5 °C (Et_2O–hexane). Anal. ($C_9H_8BrNO_2$) C, H, N. **19**: mp 127–128 °C (Et_2O); MS calcd for $C_9H_8INO_2$ 288.9599, found 288.9580. **20**: mp 106–107 °C (Et_2O). Anal. ($C_9H_8FNO_2$) C, H, N. **21**: mp 73.5–74.5 °C (Et_2O). Anal. ($C_{10}H_{11}NO_2$) C, H, N. **22**: mp 176–177.5 °C (AcOEt). Anal. ($C_9H_8N_2O_4$) C, H, N. **23**: mp 103–103.5 °C (Et_2O–hexane). Anal. ($C_9H_8ClNO_2$) C, H, N. **24**: mp 110–111 °C (Et_2O–hexane). Anal. ($C_9H_8BrNO_2$) C, H, N. **25**: mp 98–98.5 °C (Et_2O). Anal. ($C_{10}H_{11}NO_2$) C, H, N. **26**: mp 146–149 °C dec (AcOEt). Anal. ($C_9H_9NO_3$) C, H, N. **27**: mp 92–93 °C (Et_2O). Anal. ($C_9H_8ClNO_2$) C, H, N. **29**: mp 140–141 °C (acetone–hexane). Anal. ($C_9H_8INO_2$) C, H, N. **30**: mp 171–172 °C (Et_2O). Anal. ($C_9H_7I_2NO_2$) C, H, N. **36**: yield, 94%; mp 156–157 °C (benzene–hexane); $[\alpha]^{20}_D$ +37° (*c* 1, $CHCl_3$). Anal. ($C_{18}H_{14}N_2O_4$) C, H, N.

2-Chloro-5-deuteriobenzoic Acid. This was obtained by minor modification of the reported method.[17] To a solution of 5-bromo-2-chlorobenzoic acid (1.18 g, 5 mmol) and sodium carbonate (2.5 g) in D_2O (22.5 mL) was gradually added Cu–Al alloy (50:50) (1 g) at 50 °C during 5 min. After addition of the alloy, the reaction mixture was stirred at 65 °C for 8 h under an argon atmosphere, and then the insoluble materials were filtered off. The filtrate was acidified with concentrated HCl (5 mL) and extracted with AcOEt (2 × 60 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized from Et_2O–hexane to give 2-chloro-5-deuteriobenzoic acid (691 mg, 88%), mp 137–138 °C. The melting point of the unlabeled authentic compound is 142 °C: ^1H NMR (60 MHz) δ 7.48 (s, 2 H), 8.03 (s, 1 H), 9.48 (br s, 1 H); MS *m/e* (rel intensity) 156 (2.1), 157 (77.7, M^+), 159 (28.3). The product deuterium content was determined to be 97.4% by MS.

2-Chloro-5-deuteriophenylacetic Acid. This was obtained from 2-chloro-5-deuteriobenzoic acid by the reported Arndt–Eistert one-carbon elongation method:[32] yield, 75%; mp 94–96 °C (benzene–hexane). The melting point of the unlabeled authentic compound is 95–97 °C: ^1H NMR (60 MHz) δ 3.80 (s, 2 H), 7.10–7.54 (m, 3 H), 10.46 (br s, 1 H); MS *m/e* (rel intensity) 170 (1.0), 171 (42.5, M^+), 173 (14.9). The product deuterium content was determined to be 97.6% by MS.

2-(2-Chloro-5-deuteriophenyl)-*N*-methoxyacetamide (31). This was obtained from 2-chloro-5-deuteriophenylacetic acid by the method A for the preparation of *N*-methoxyamide: yield, 98%; mp 110–112 °C ($CHCl_3$–hexane). The melting point of the unlabeled authentic compound **10** is 113–114 °C: ^1H NMR (60 MHz) δ 3.63 (s, 2 H), 3.70 (s, 3 H), 7.09–7.50 (m, 3 H), 8.72 (br s, 1 H); IR (Nujol) 1660, 3170 cm^{-1}; MS *m/e* (rel intensity) 164 (1.0), 165 (44.4, $M^+ - Cl$), 126 (100). The product deuterium content was determined to be 97.7% by MS.

Cyclization of 31. The procedure was the same as the cyclization of **10**, and the products were separated by column chromatography on silica gel. Elution with Et_2O–hexane (2:1) afforded **32** and **17** (total yield, 72%); mp 77–78 °C (Et_2O–hexane). The melting point of the unlabeled authentic compound **17** is 77–78 °C: ^1H NMR (CD_3COCD_3, 270 MHz) δ 3.51 (s, 2 H), 3.99 (s, 3 H), 6.98 (d, 0.24 H, J = 8.1 Hz), 7.08 (d, 1 H, J = 7.8 Hz), 7.34–7.37 (m, 1 H); IR (Nujol) 1730 cm^{-1}; MS *m/e* (rel intensity) 197 (25.7), 198 (86.3, M^+), 200 (30.4). The product deuterium content was determined to be 76.5% by MS. Further elution afforded **33**: yield, 12%; mp 103–104 °C (Et_2O–hexane). The melting point of the unlabeled authentic sample **23** is 103–104 °C: ^1H NMR (CD_3COCD_3, 270 MHz) δ 3.55 (s, 2 H), 3.98 (s, 3 H), 7.25 (s, 1 H), 7.29 (s, 1 H); IR (Nujol) 1730 cm^{-1}; MS *m/e* (rel intensity) 197 (2.9), 198 (87.0, M^+), 200 (33.0). The product deuterium content was determined to be 96.8% by MS.

Cyclization of *N*-Methoxy-4-phenylbutyramide. The procedure was the same as just above, and the products were separated by column chromatography on silica gel. First elution with benzene–AcOEt (5:1) afforded **5**: yield, 60%; bp 150 °C (1 mmHg) (bath temperature); mp 45–46 °C; lit.[18] bp 145 °C (0.5 mmHg). The spectra match literature data.[18] Second elution with CH_2Cl_2–MeOH (50:1) afforded **41** (35%) as a colorless oil, which was subjected to the next DDQ oxidation: ^1H NMR (60 MHz) δ 1.70–2.20 (m, 4 H), 2.03 (s, 1 H), 2.30–2.73 (m, 2 H), 3.62 + 3.72 (s, 3 H), 4.39 + 4.57 (br s, 1 H), 5.67–6.30 (m, 4 H); IR (neat) 1660, 3350 cm^{-1}.

DDQ Oxidation of 41. A solution of **41** (195.5 mg, 0.93 mmol) and DDQ (276 mg, 1.2 mmol) in dioxane (5 mL) was stirred at room temperature for 26 h. The precipitated solid was filtered off, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a column of silica gel with CH_2Cl_2–MeOH (50:1) as the eluent to give **39c** (177 mg, 92%). The same material was formed from the reaction of **38c** (vide post).

3-Amino-3,4-dihydro-1-methoxycarbostyril (37). A solution of **36** (1.17 g, 3.6 mmol) and 80% hydrazine hydrate (681 mg, 10.8 mmol) in EtOH (20 mL) was heated at 80 °C for 20 min. The reaction mixture was then concentrated under reduced pressure, and the residue was extracted with $CHCl_3$ (2 × 50 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel with CH_2Cl_2–MeOH (20:1) as the eluent to give **37** (642 mg, 92%) as a oil: $[\alpha]^{19}_D$ –37.4° (*c* 5, $CHCl_3$); ^1H NMR (60 MHz) δ 1.97 (br s, 2 H), 2.90–3.20 (m, 2 H), 3.65 (dd, 1 H, J = 8.0, 14.0 Hz), 3.87 (s, 3 H), 7.07–7.40 (m, 4 H); IR (neat) 1700, 3300, 3375 cm^{-1}; MS *m/e* 192 (M^+). The hydrochloride: mp 205–207 °C (EtOH–Et_2O); $[\alpha]^{19}_D$ –22.0° (*c* 1, H_2O). Anal. ($C_{10}H_{12}N_2O_2$·HCl) C, H, N.

Catalytic Reduction of 1-Methoxy-2-oxindoles Using 10% Pd on Carbon. General Procedure. A solution of a 1-methoxy-2-oxindole (1 mmol) in MeOH (10 mL) containing 100 mg of 10% Pd–C was hydrogenated until the reaction was complete. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with benzene–AcOEt as the eluent to give the corresponding 2-oxindole. **1,3-Dihydro-2*H*-benz[*e*]indol-2-one**: yield, 84%; mp 231–233 °C (lit.[45] mp 234 °C). **1,3-Dihydro-2*H*-benz[*c*]indol-2-one**: yield, 87%; mp 246–248 °C (lit.[45] mp 245 °C). **5,6-Dimethoxy-2-oxindole**: yield, 88%; mp 208.5 °C dec (lit.[46] mp 210 °C). **6-Methyl-2-oxindole**: yield, 87%; mp 177–178 °C (lit.[47] mp 171–173 °C). **4-Methyl-2-oxindole**: yield, 92%; mp 208–209 °C (lit.[48] mp 211–212 °C). The spectra match literature data.[48] **7-Methyl-2-oxindole**: yield, 98%; mp 205–206.5 °C (lit.[49] mp 208 °C). The spectra match literature data.[49] **5-Hydroxy-2-oxindole**: yield, 72%; mp 263–266 °C dec (lit.[50] mp 265–266 °C dec). The spectra match literature data.[50] **5-Methoxy-2-oxindole**: yield, 81%; mp 151–153 °C (lit.[50] mp 152–154 °C). **6-Methoxy-2-oxindole**: yield, 94%; mp 156.5–158.5 °C (lit.[50] mp 158 °C).

General Procedure for Methylation of 1-Methoxy-2-oxindoles (Chart III). To a solution of a 1-methoxy-2-oxindole (1 mmol) in acetone (5 mL) was added powdered KOH (280 mg, 5 mmol). After a few minutes, methyl iodide (0.14 mL, 2.2 mmol) was added to the solution, and the reaction mixture was refluxed for 5 min. After the reaction was complete, benzene (30 mL) was added to the reaction mixture and insoluble materials were re-

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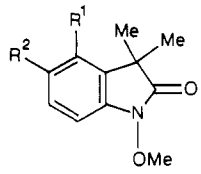
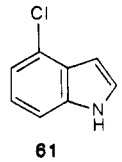
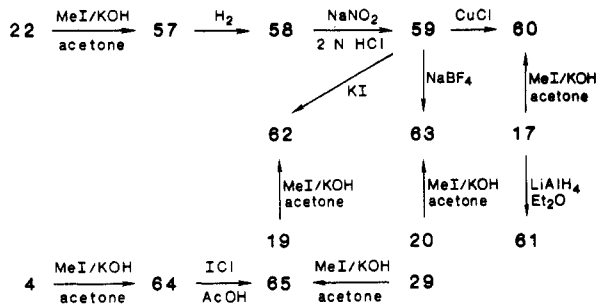
Chart III



57: $R^1 = NO_2$; $R^2 = H$ **62**: $R^1 = I$; $R^2 = H$
58: $R^1 = NH_2$; $R^2 = H$ **63**: $R^1 = F$; $R^2 = H$
59: $R^1 = N_2^+Cl^-$; $R^2 = H$ **64**: $R^1 = R^2 = H$
60: $R^1 = Cl$; $R^2 = H$ **65**: $R^1 = H$; $R^2 = I$



61



moved by filtration. The benzene solution was washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel with benzene–AcOEt (10:1) as the eluent to give the corresponding 3,3-dimethyl-1-methoxy-2-oxindole. **57**: yield, 86%; mp 116–117 °C (benzene). Anal. ($C_{11}H_{12}N_2O_4$) C, H, N. **60**: yield, 98%; a colorless oil; bp 150 °C (5 mmHg) (bath temperature). Anal. ($C_{11}H_{12}ClNO_2$) C, H, N. **62**: yield, 92%; mp 31–32 °C (cold hexane). Anal. ($C_{11}H_{12}INO_2$) C, H, N. **63**: yield, 93%; mp 49–49.5 °C (hexane); MS calcd for $C_{11}H_{12}FNO_2$ 209.0852, found 209.0882. **64**: yield, 99%; mp 43–44.5 °C (hexane). Anal. ($C_{11}H_{13}NO_2$) C, H, N. **65**: yield, 82%; mp 81–82 °C (hexane). Anal. ($C_{11}H_{12}INO_2$) C, H, N.

4-Amino-3,3-dimethyl-1-methoxy-2-oxindole (58). Compound **57** (335 mg, 1.42 mmol) in MeOH (20 mL) containing 60 mg of 10% Pd–C was hydrogenated for 15 min. After the usual workup, the crude product was chromatographed on a column of silica gel with CH_2Cl_2–MeOH (100:1) as the eluent to give **58** (249 mg, 85%); mp 165–166 °C (CH_2Cl_2–hexane); ^1H NMR (270 MHz) δ 1.50 (s, 6 H), 3.72 (br, 2 H), 3.97 (s, 3 H), 6.37 (d, 1 H, J = 8.2 Hz), 6.47 (d, 1 H, J = 8.2 Hz), 7.08 (t, 1 H, J = 8.2 Hz); IR (Nujol) 1710, 3380, 3470 cm^{-1}; MS m/e 206 (M^+). Anal. ($C_{11}H_{14}N_2O_2$) C, H, N.

4-Chloro-3,3-dimethyl-1-methoxy-2-oxindole (60). This was obtained from **58** by the reported method:[51] yield, 68%. This was identical with the authentic sample obtained by the methylation of **17**.

3,3-Dimethyl-4-iodo-1-methoxy-2-oxindole (62). This was obtained from **58** by the reported method:[51] yield, 98%. This was identical with the authentic sample obtained by the methylation of **19**.

3,3-Dimethyl-4-fluoro-1-methoxy-2-oxindole (63). This was obtained from **58** by the reported method:[51] yield, 62%. This was identical with the authentic sample obtained by the methylation of **20**.

3,3-Dimethyl-5-iodo-1-methoxy-2-oxindole (65). To a stirred solution of **64** (151 mg, 0.79 mmol) in acetic acid (2 mL) was added a solution of iodine monochloride (154 mg, 0.95 mmol) in acetic acid (1 mL) slowly. The reaction mixture was stirred at room temperature for 3.5 h and then diluted with CH_2Cl_2 (50 mL) and 5% Na_2CO_3 (30 mL). The separated organic solution was washed with 5% $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel with benzene–AcOEt (10:1) as the eluent to give **65** (193 mg, 77%), which was identical with the authentic sample obtained by the methylation of **29**.

5-Bromo-1-methoxy-2-oxindole (66). This was prepared from 1-methoxy-2-oxindole by the reported method:[26] mp 117–119 °C (lit.[26] mp 118–120 °C); ^1H NMR (CD_3COCD_3, 270 MHz) δ 3.55 (s, 2 H), 3.98 (s, 3 H), 6.96 (d, 1 H, J = 8.1 Hz), 7.45 (s, 1 H), 7.49 (d, 1 H, J = 8.1 Hz).

4-Chloroindole (61). To a stirred suspension of $LiAlH_4$ (101 mg, 2.66 mmol) in anhydrous Et_2O (5 mL) was added a solution of 4-chloro-2-oxindole (**17**) (175 mg, 0.89 mmol) in anhydrous Et_2O (5 mL) slowly, and the mixture was then refluxed for 3 h. After the usual workup, the resulting crude product was purified by column chromatography on silica gel with CH_2Cl_2–hexane (3:7) as the eluent to give **61** (53.3 mg, 40%), which was identical with the authentic sample:[52] bp 119 °C (6 mmHg) [lit.[52] bp 143 °C (10 mmHg)]; ^1H NMR (60 MHz) δ 6.67 (t, 1 H, J = 2.9 Hz), 7.07–7.35 (m, 4 H), 8.27 (br s, 1 H, NH); IR (neat) 3450 cm^{-1}.

3-(Hydroxyimino)-4-iodo-1-methoxy-2-oxindole. 4-Amino-1-methoxy-2-oxindole was prepared from **22** by the same method as described for the preparation of **58**: yield, 85%; ^1H NMR (60 MHz, $CDCl_3$–CD_3OD) δ 3.28 (s, 2 H), 3.40 (br s, 2 H), 3.97 (s, 3 H), 6.43 (d, 2 H, J = 9.0 Hz), 7.10 (t, 1 H, J = 9.0 Hz); IR (Nujol) 1720, 3220, 3350 cm^{-1}; MS m/e 178 (M^+). The diazotization of 4-amino-1-methoxy-2-oxindole (101.4 mg, 0.57 mmol) with $NaNO_2$ (86.5 mg, 1.25 mmol) and subsequent iodination (KI, 2.4 g) were done by the same method as described for the preparation of **62**. The crude product was chromatographed on a column of silica gel with benzene–AcOEt (10:1) as the eluent to give 3-(hydroxyimino)-4-iodo-1-methoxy-2-oxindole (63.2 mg, 35%): mp 135–137 °C (CH_2Cl_2–hexane); ^1H NMR (60 MHz) δ 4.10 (s, 3 H), 6.98–7.73 (m, 3 H), 13.47 (s, 1 H); IR (Nujol) 1725, 3200 cm^{-1}; MS m/e 318 (M^+); MS calcd for $C_9H_7IN_2O_3$ 317.9500, found 317.9532.

Reaction of *N*-Chloro-*N*-methoxy-2-phenylacetamide with $AgBF_4$ in Benzene. A solution of *N*-chloro-*N*-methoxy-2-phenylacetamide (307 mg, 1.5 mmol) and $AgBF_4$ (330 mg, 1.65 mmol) in dry benzene (8 mL) was stirred in the dark at room temperature for 24 h. After the usual workup, the products were separated by column chromatography on silica gel. First elution with benzene–hexane (5:1) afforded *N*-methoxy-*N*-phenyl-2-phenylacetamide (120 mg, 32%) as a colorless oil: ^1H NMR (60 MHz) δ 3.62 (s, 3 H), 3.90 (s, 2 H), 7.13–7.60 (m, 5 H), 7.30 (s, 5 H); IR (neat) 1680 cm^{-1}; MS m/e 241 (M^+); MS calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1117. Further elution afforded **4** (39 mg, 15%), which was identical with the authentic sample.

Reaction of *N*-Chloro-*N*-methoxy-2-phenylacetamide with $AgBF_4$ in MeOH. A solution of *N*-chloro-*N*-methoxy-2-phenylacetamide (365 mg, 1.8 mmol) and $AgBF_4$ (405 mg, 2.1 mmol) in absolute MeOH (20 mL) was stirred in the dark at room temperature for 24 h. After the usual workup, the crude product was purified by column chromatography on silica gel eluting with benzene to give methyl phenylacetate (252 mg, 92%), which was identical with the commercial material.

General Procedure for the Syntheses of Spiro Lactams. The procedure was the same as the general procedure for the cyclization of *N*-chloro-*N*-methoxyamides (vide ante). **39a**: mp 105–106 °C [$CHCl_3$–(*i*-Pr)$_2$O]. Anal. ($C_9H_9NO_3$) C, H, N. **39b**: mp 127–128 °C [$CHCl_3$–(*i*-Pr)$_2$O] (lit.[18] mp 125–127 °C). **39c**: mp 110–111 °C (lit.[18] mp 104.5–106 °C). **39d**: mp 216–217 °C [$CHCl_3$–(*i*-Pr)$_2$O]; $[\alpha]^{28}_D$ –171.1° (*c* 1, $CHCl_3$). Anal. ($C_{18}H_{14}N_2O_5$) C, H, N. **39e**: mp 86–87 °C (benzene–hexane). Anal. ($C_{10}H_{11}NO_3$) C, H, N. **39f**: mp 76–77 °C (benzene–hexane). Anal. ($C_{11}H_{13}NO_3$) C, H, N. **39g**: mp 121–122 °C (Et_2O). Anal. ($C_9H_7NO_4Cl_2$) C, H, N. **39h**: a colorless oil; MS calcd for $C_{10}H_{11}NO_3$ 193.0738, found 193.0758.

6-(Hydroxyimino)-1-methoxy-1-azaspiro[4.5]decan-2-one. Compound **39h** (172.5 mg, 0.89 mmol) in AcOEt (10 mL) was hydrogenated in the presence of 10% Pd–C (35 mg). After the usual workup, the crude product was chromatographed on a column of silica gel with AcOEt–hexane (1:6) as the eluent to give

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1-methoxy-1-azaspiro[4.5]decane-2,6-dione (129 mg, 73%) as a oil, which was directly subjected to the next reaction: ^{1}H NMR (60 MHz) δ 1.63–2.80 (m, 12 H), 3.97 (s, 3 H); IR (neat) 1700, 3200 cm^{-1}; MS m/e 197 (M^+). To a mixture of 1-methoxy-1-azaspiro[4.5]decane-2,6-dione (74 mg, 0.38 mmol) and hydroxylamine hydrochloride (47 mg, 0.56 mmol) in EtOH (1 mL) was added pyridine (1 mL) with cooling. The reaction mixture was stirred at room temperature for 5 h. After the usual workup, the crude product was purified by column chromatography on silica gel, eluting with benzene–AcOEt (1:2) to give 6-(hydroxyimino)-1-methoxy-1-azaspiro[4.5]decan-2-one (55 mg, 69%): mp 181–183 °C (AcOEt); ^{1}H NMR (270 MHz) δ 1.40–1.64 (m, 2 H), 1.81–1.92 (m, 5 H), 2.13–2.34 (m, 4 H), 3.35–3.42 (m, 1 H), 3.87 (s, 3 H), 7.69 (s, 1 H); IR (Nujol) 1700, 3200 cm^{-1}. Anal. ($C_{10}H_{16}N_2O_3$) C, H, N.

Reaction of *N*-Chloro-*N*-methoxy-2-(4-methoxyphenyl)-acetamide with $AgBF_4$ in Et_2O. A solution of *N*-chloro-*N*-methoxy-2-(4-methoxyphenyl)acetamide (1.18 g, 5.1 mmol) and $AgBF_4$ (1.2 g, 6.2 mmol) in absolute Et_2O (60 mL) was stirred in the dark at room temperature for 24 h. After the usual workup, the products were separated by column chromatography on silica gel, eluting with benzene–AcOEt (2:1). The first fraction afforded a mixture of **43** and **44**, which were separated by recrystallization from benzene–hexane. **43**: 18.6 mg (1.8%); mp 114–116 °C (lit.[22] mp 121–122 °C); ^{1}H NMR (CD_3COCD_3, 270 MHz) δ 3.40 (s, 2 H), 3.82 (s, 3 H), 3.97 (s, 3 H), 6.58 (dd, 1 H, J = 2.2, 8.4 Hz), 6.60 (s, 1 H), 7.16 (d, 1 H, J = 8.4 Hz); IR (KBr) 1710 cm^{-1}; MS m/e 193 (M^+). **44**: 37.6 mg (3.2%); mp 174–176 °C (lit.[18] mp 176–178 °C). The spectra match literature data.[18] The structure of **44** was determined by the comparison with the authentic sample prepared by the chlorination of **43** (vide post). The second fraction afforded **42** (22.1 mg, 2.2%): mp 74–76 °C (lit.[18] mp 78–79 °C). The spectra match literature data.[18] The structures of **42** and **43** were confirmed by transformation to the corresponding 2-oxindoles. The third fraction afforded **39a** (231.2 mg, 25%), which was identical with the compound obtained by the spiro cyclization of **38a** (vide ante).

Chlorination of 43. A solution of **43** (53.6 mg, 0.28 mmol) and NCS (48.2 mg, 0.36 mmol) in AcOH (2 mL) was stirred at room temperature for 1 h and then heated at 60 °C for 2 h. After being cooled in an ice bath, the mixture was added to 10% Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. Elution with benzene–AcOEt (3:1) afforded 3,5-dichloro-1,6-dimethoxy-2-oxindole (14.7 mg, 20%): mp 154–155 °C; ^{1}H NMR (CD_3COCD_3, 270 MHz) δ 4.01 (s, 3 H), 4.02 (s, 3 H), 5.43 (s, 1 H), 6.95 (s, 1 H), 7.49 (s, 1 H); IR (Nujol) 1750 cm^{-1}; MS m/e 261 + 263 + 265 (9:6:1) (M^+); MS calcd for $C_{10}H_9Cl_2NO_3$ 260.9959, found 260.9967. Further elution afforded **44** (40.4 mg, 64%): mp 175–177 °C (benzene–hexane). This was identical with the compound **44** obtained by the above reaction.

General Procedure for the Intermolecular Methoxyamidation of Arenes with *N*-Chloro-*N*-methoxyamides. A solution of an arene (10–20 mmol) and silver carbonate (1.1 g, 4 mmol) in TFA (5 mL) was added to *N*-chloro-*N*-methoxyamide (2 mmol) cooled in an ice bath. The stirring was continued for 30 min to complete the reaction, and then the solvent was removed under reduced pressure below 35 °C. After the usual workup, the crude product was purified by column chromatography on silica gel, eluting with benzene–AcOEt, to give the corresponding *N*-methoxy-*N*-phenylamide. **47a**: yield, 93%; a colorless oil; bp 180 °C (2 mmHg) (bath temperature); ^{1}H NMR (60 MHz) δ 0.70–2.70 (m, 15 H), 3.68 (s, 3 H), 7.10–7.50 (m, 5 H); IR (neat) 1680 cm^{-1}; MS m/e 249 (M^+). Anal. ($C_{15}H_{23}NO_2$) C, H, N. **47b**: yield, 71%; mp 50–52 °C (lit.[53] mp 54.5–55 °C). **47c**: yield, 88%; bp 200 °C (3 mmHg) (bath temperature). The spectra match literature data.[54]

***tert*-Butyl *N*-Methoxy-*N*-phenylcarbamate (47d).** This was obtained in 51% yield from **46d** and benzene by the similar procedure as described above in TFA and $MeNO_2$ (1:5). The spectra match literature data.[54]

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Intermolecular Reaction of Toluene with 46a. According to a procedure similar to the general procedure mentioned above, the reaction of **46a** (229 mg, 1.1 mmol) and toluene (0.59 mL, 5.5 mmol) gave a colorless oil (248 mg), which was indicated to be a mixture of three isomers (**48a**, **48b**, and **48c**) by VPC (column A). The products were hydrogenated to give in 96% yield the corresponding octanamides which were identified by VPC (column B) with the authentic samples prepared by the Schotten–Baumann reaction of *o*-, *m*-, and *p*-methylaniline and octanoyl chloride. The product ratio was determined at this stage to be 45% of **48a**, 11% of **48b**, and 45% of **48c** by VPC (column B).

Intermolecular Reaction of *p*-Xylene with 46a. According to a procedure similar to the general procedure mentioned above, the reaction of **46a** (2.25 g, 10.8 mmol) and *p*-xylene (5.76 g, 54.3 mmol) gave **49a** (2.25 g, 75%) as a colorless oil: ^{1}H NMR (60 MHz) δ 0.70–2.40 (m, 21 H), 3.64 (s, 3 H), 7.05–7.40 (m, 4 H); IR (neat) 1670 cm^{-1}; MS m/e 227 (M^+); MS calcd for $C_{17}H_{27}NO_2$ 227.2043, found 227.2056. Compound **49a** was hydrogenated to give in 95% yield *N*-(2,5-dimethylphenyl)octanamide in which 4% of *N*-(2,4-dimethylphenyl)octanamide was found to be contaminated by VPC (column B), compared with the authentic samples prepared by the Schotten–Baumann reaction of 2,5- and 2,4-dimethylaniline and octanoyl chloride.

Intermolecular Reaction of Anisole with 46a. The reaction of **46a** (277 mg, 1.33 mmol) and anisole (0.73 mL, 6.67 mmol) was done by the similar procedure as above in TFA and $MeNO_2$ (1:4). The products were separated by column chromatography on silica gel. First elution with benzene–AcOEt (20:1) afforded **50a** (186 mg, 50%) as a colorless oil: ^{1}H NMR (60 MHz) δ 0.70–2.60 (m, 15 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 6.80–7.60 (m, 4 H); IR (neat) 1680 cm^{-1}; MS m/e 279 (M^+); MS calcd for $C_{16}H_{25}NO_3$ 279.1836, found 279.1831. Second elution with benzene–AcOEt (10:1) afforded **50b** (112 mg, 30%) as a colorless oil: ^{1}H NMR (60 MHz) δ 0.70–2.70 (m, 15 H), 3.64 (s, 3 H), 3.77 (s, 3 H), 6.86 (d, 2 H, J = 8.6 Hz), 7.31 (d, 2 H, J = 8.6 Hz); IR (neat) 1680 cm^{-1}; MS m/e 279 (M^+); MS calcd for $C_{16}H_{25}NO_3$ 279.1836, found 279.1855. Compounds **50a** and **50b** were hydrogenated to give the corresponding octanamides, which were identified by VPC (column B) with the authentic samples prepared by the Schotten–Baumann reaction of *o*- and *p*-anisidine and octanoyl chloride.

Intermolecular Reaction of Naphthalene with 46a. The reaction of **46a** (264 mg, 1.27 mmol) and naphthalene (815 mg, 6.36 mmol) was done by the similar procedure as above in TFA and $MeNO_2$ (1:1). The products were separated by column chromatography on silica gel. Elution with benzene–AcOEt (50:1) afforded **51b** (55 mg, 11%) as a colorless oil: ^{1}H NMR (60 MHz) δ 0.60–2.80 (m, 15 H), 3.84 (s, 3 H), 7.30–7.80 (m, 7 H); IR (neat) 1680 cm^{-1}; MS m/e 299 (M^+). MS calcd for $C_{19}H_{25}NO_2$ 299.1887, found 299.1895. Further elution afforded **51a** (402 mg, 80%) as a colorless oil: ^{1}H NMR (60 MHz) δ 0.60–2.60 (m, 15 H), 3.71 (s, 3 H), 7.20–7.90 (m, 7 H); IR (neat) 1680 cm^{-1}; MS m/e 299 (M^+); MS calcd for $C_{19}H_{25}NO_2$ 299.1887, found 299.1904. Compounds **51a** and **51b** were hydrogenated to give the corresponding octanamides, which were identified by VPC (column B) with the authentic samples prepared by the Schotten–Baumann reaction of 1- and 2-naphthylamine and octanoyl chloride.

Cyclization of *N*-Chloro-*N*-methoxy-3-phenylpropionamide (2) with Silver Sulfate. (a) Under a Nitrogen Atmosphere. A solution of **2** (0.7 mmol) with Ag_2SO_4 (1.4 mmol) in TFA (5.5 mL) was stirred at 0 °C in the dark under a nitrogen atmosphere. In 1 h, all the starting material disappeared. After the usual workup, **3** was isolated in 78% yield.

(b) In the Presence of DPPH. A solution of **2** (0.7 mmol) with Ag_2SO_4 (1.4 mmol) in TFA (5.5 mL) containing DPPH (0.07 mmol) was stirred at 0 °C in the dark under a nitrogen atmosphere.

(c) Under an Oxygen Atmosphere. A solution of **2** (0.7 mmol) with Ag_2SO_4 (1.4 mmol) in TFA (5.5 mL) was stirred at 0 °C in the dark under an oxygen atmosphere. The results are summarized in Table V.

Supplementary Material Available: ^{1}H NMR and IR data of *N*-chloro-*N*-methoxyamides, 1-methoxy-2-oxindoles, and 3,3-dimethyl-1-methoxy-2-oxindoles, ^{1}H and ^{13}C NMR and IR data of spiro lactams, and analytical data (11 pages). Ordering information is given on any current masthead page.