Exploratory Synthetic Studies of the α-Methoxylation of Amides *via* Cuprous Ion-Promoted Decomposition of *o*-Diazobenzamides†

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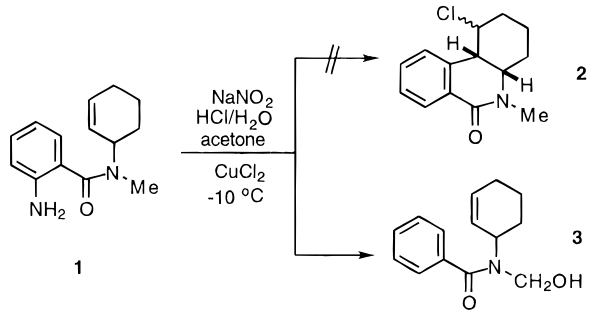
Received August 6, 1996⊗

A convenient nonelectrochemical amide oxidation method has been developed. The process involves a cuprous ion-promoted decomposition of *o*-diazobenzamides like **4**, generated *in situ* from the corresponding *o*-aminobenzamides, to give *N*-acyliminium ion intermediate **9** via a 1,5-*H*-atom transfer, followed by metal-catalyzed oxidation of the resulting α-amidyl radical. The transformation produces α-methoxybenzamides **15** in good yields. An attempt was made to apply this oxidation method to a total synthesis of the alkaloid (−)-anisomycin (**16**). Scalemic *o*-aminobenzamide pyrrolidine derivatives **18a**/**18b** underwent oxidation to give α-methoxylated amide substrates **19a**/**19b**, respectively, in good yields. However, alkylation of the *N*-acyliminium intermediate **20** with (*p*-methoxybenzyl)magnesium chloride gave the undesired *anti*-compounds **22a**/**22b** as the major products. The amide oxidation exhibits good regioselectivity with many unsymmetrical 2-substituted piperidine and pyrrolidine systems. In general, it appears that the larger the *C*-2 substituent, the greater the methylene/methine *H*-atom abstraction ratio. A mechanistic rationale for this selectivity is suggested based upon amide rotamer populations. An extension of this methodology can be used to conduct two sequential amide oxidations using readily prepared 2-amino-6-nitrobenzamides such as **68** and **69**.

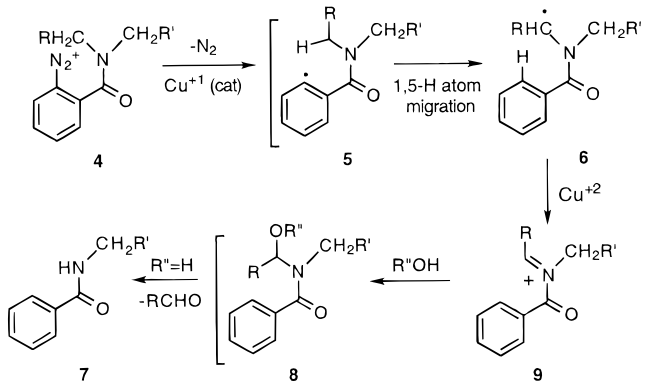
Introduction

During the course of our recent work on total synthesis of the *Amaryllidaceae* alkaloid lycoricidine and its congeners,[1] we explored an approach to the tricyclic ring system of the natural products using an intramolecular Meerwein arylation as the key strategic step.[2,3] However, exposure of the simple model *o*-aminobenzamide **1** to the usual Meerwein arylation conditions[2] did not produce any of the desired tricycle **2** (Scheme 1) but rather chromatography of the complex reaction mixture led to isolation of only the *N*-hydroxymethyl amide **3**, albeit in low yield. A search of the literature indicated that this transformation is not unprecedented. In fact, over four decades ago Hey and Turpin found that an *o*-diazobenzamide **4** prepared from a secondary amine can be dealkylated to a benzamide **7** upon treatment with copper powder under aqueous conditions (Scheme 2).[4] In a series of elegant papers, Cohen and co-workers subsequently established that this transformation is catalyzed by Cu^{+1} ion and provided strong evidence for the free radical mechanism shown in Scheme 2.[5] The proposed reaction sequence involves initial reduction of the diazonium salt by Cu^{+1} leading to evolution of nitrogen and formation of an aryl radical **5**, along with Cu^{+2} ion.[2c] Radical **5** then undergoes a 1,5-hydrogen atom transfer to generate α-amidyl radical **6**, which is oxidized by cupric ion to the *N*-

Scheme 1



Scheme 2



† Dedicated to Professor Richard W. Franck on the occasion of his 60th birthday.

‡ Author to be contacted regarding X-ray structure determination.

⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1996.

(1) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823.

(2) For reviews of the Meerwein arylation, see: (a) Rondestvedt, C. S., Jr. *Org. React.* **1960**, *11*, 189. (b) Rondestvedt, C. S., Jr. *Ibid.* **1976**, *24*, 225. (c) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(3) See also: Murphy, J. A.; Rasheed, F.; Roome, S. J.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1996**, *737* and references cited therein.

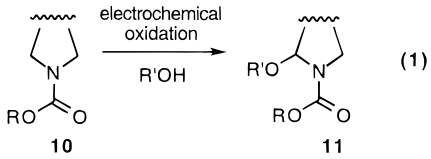
(4) Hey, D. H.; Turpin, D. G. *J. Chem. Soc.* **1954**, 2471. See also, Hey, D. H.; Rees, C. W.; Todd, A. R. *J. Chem. Soc. (C)* **1967**, 1518 and references cited therein.

(5) (a) Lewin, A. H.; Dinwoodie, A. H.; Cohen, T. *Tetrahedron* **1966**, *22*, 1527. (b) Cohen, T.; McMullen, C. H.; Smith, K. *J. Am. Chem. Soc.* **1968**, *90*, 6866. (c) Cohen, T.; Smith, K. W.; Swendloff, M. D. *Ibid.* **1971**, *93*, 4303. For a related free radical process involving sulfonamides, see: Pines, S. H.; Purick, R. M.; Reamer, R. A.; Gal, G. *J. Org. Chem.* **1978**, *43*, 1337.

S0022-3263(96)01529-0 CCC: $12.00

acyliminium species **9**. Such imines are highly electrophilic and are prone to hydrolysis *via* a "methylol" such as **8** (R″ = H) to afford the dealkylated product **7**.[6]

N-Acyliminium compounds **9** are now well established as important synthons in organic chemistry.[7,8] The most common method presently used for generating these intermediates is by elimination of α-alkoxy amides of type **8** (R″ = Me, Et, *etc.*). Although it is now possible to prepare precursors **8** directly from the component amides and aldehydes,[9] a very simple route to these species involves electrochemical anodic oxidation of carbamates and related *N*-acyl derivatives **10** of amines (eq 1). This latter procedure to α-alkoxy carbamates **11** has been widely investigated by Shono and co-workers and has been used extensively in alkaloid total synthesis.[8a]



(1)

A very attractive aspect of the amide oxidation methodology is that it allows functionalization of a generally stable and often readily available starting material.[10] It occurred to us that the Hey/Turpin/Cohen chemistry outlined in Scheme 2 might provide a convenient alternative to the Shono electrochemical amide oxidation procedure in eq 1 and in this paper are described our feasibility studies toward this objective.[11]

Results and Discussion

A. Development of Methodology with Symmetrical Systems. Initial studies were directed at developing an experimentally simple and convenient two-step protocol for amide oxidations. It is well known that a secondary amine **13** can be converted in high isolated yield into an *o*-aminobenzamide derivative **14** using commercially available isatoic anhydride (**12**)[12] (Scheme 3). In certain cases involving less basic and/or hindered amines an alternative two-step procedure has been used (*vide infra*). It is possible to combine the diazotization step with the Hey/Turpin/Cohen sequence to produce an α-alkoxybenzamide **15** from the *o*-aminobenzamide. Thus, treatment of **14** with sodium nitrite and dry HCl in methanol containing about 5% cuprous chloride for varying lengths of time at room temperature yields products **15** in good yields. A number of examples of this sequence are shown in Table 1.

Scheme 3

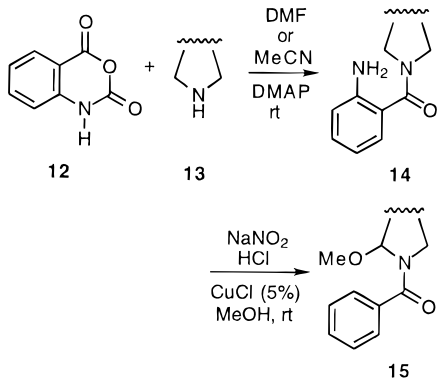


Table 1. Conversion of Symmetrical Secondary Amines to α-Methoxybenzamides

Secondary Amine	*o*-Aminobenzamide (yield %)	Oxidation Reaction Time	Product(s) (yield %)
pyrrolidine	**14a** (92)	1.5 h	**15a** (43)
		2 d	**15a'** (82)
piperidine	**14b** (93)	1.5 h	**15b** (69)
		3 d	**15b'** (49)
morpholine	**14c** (91)	27 h	**15c** (68)
2,6-dimethylmorpholine	**14d** (90)	3 d	**15d** (71)
homopiperidine	**14e** (85)	2 h	**15e** (73)
diethylamine	**14f** (67)	1 h	**15f** (86) (4)

In the case of the pyrrolidine-derived system, ring opening of α-methoxybenzamide **15a** tends to occur, particularly if extended reaction times are used.[8] Therefore, the amido acetal **15a'** can be isolated in good yield if the oxidation step is conducted for two days. The six- and seven-membered ring systems do not show quite as great a propensity for *in situ* acetal formation but do form

(6) "Methylol" derivatives of formaldehyde such as **3** or of other electrophilic aldehydes are often isolable. *cf* . Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

(7) See for example: Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525. Zaugg, H. E. *Synthesis* **1970**, 49 and 181. Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. Hiemstra, H.; Speckamp, W. N. Additions to *N*-Acyl Iminium Ions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 1047.

(8) (a) Shono, T. *Top. Curr. Chem.* **1988**, *148*, 131. Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*"; Springer: Heidelberg, 1984, and references cited therein. (b) Mitzlaff, M.; Warning, K.; Jensen, H. *Liebigs Ann. Chem.* **1978**, 1713.

(9) Johnson, A. P.; Luke, R. W. A.; Steele, R. W.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 883. Johnson, A. P.; Luke, R. W. A.; Boa, A. N. *Ibid.* **1996**, 895 and references cited therein.

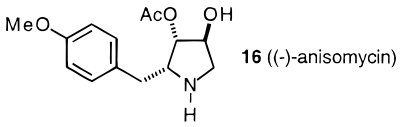
(10) See also: Magnus, P.; Hulme, C.; Weber, W. *J. Am. Chem. Soc.* **1994**, *116*, 4501.

(11) For preliminary accounts of portions of this work, see: (a) Han, G.; McIntosh, M. C.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 5813. (b) Weinreb, S. M. *J. Heterocycl. Chem.* **1996**, *33*, 1437.

(12) Venuti, M. C. *Synthesis* **1982**, 266. Coppola, G. M. *Ibid.* **1980**, 505. Staiger, R. P.; Wagner, E. C. *J. Org. Chem.* **1953**, *18*, 1427.

analogous products, although more slowly. The acyclic system **14f** is prone to dealkylation unless care is taken to exclude traces of water. However, in the presence of 4 Å molecular sieves, α-methoxybenzamide **15f** is produced in high yield. It might be noted that acyclic α-alkoxyamides like **15f** generally appear to be hydrolytically sensitive and tend to decompose easily under the conditions used in this methodology. This dealkylation also appears to be an occasional problem in the electrochemical procedure.[8]

In view of the successful development of the fundamental oxidation methodology with symmetrical systems, we decided to next investigate an application of this procedure to a total synthesis of (−)-anisomycin (**16**),[13] an alkaloid produced by a *Streptomyces* species.[14] This



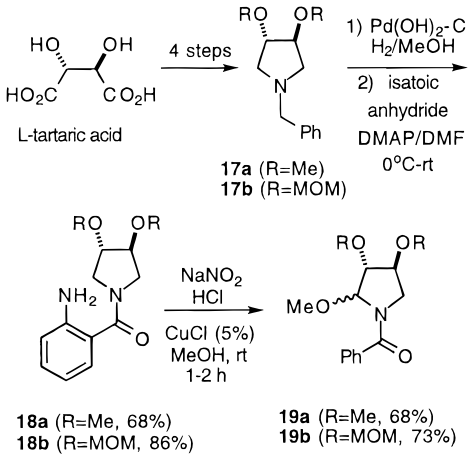
16 ((-)-anisomycin)

compound has antibiotic activity against both pathogenic protozoa and some fungi, and has been used clinically for treatment of tricomonas vaginitis and amoebic dysentery.[15] Although there are over a dozen existing syntheses of this alkaloid,[16] both in racemic form and of the (−)- and (+)-enantiomers, it appeared that our methodology might provide a very direct new entry to anisomycin.

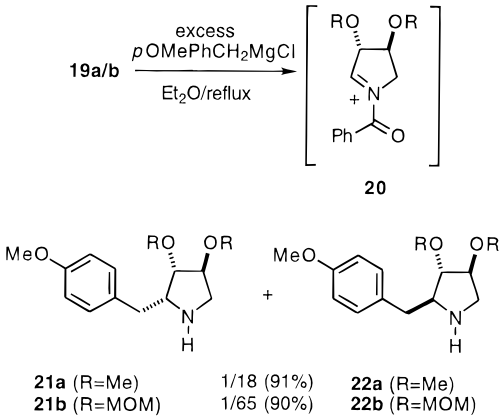
The substrates utilized in our study were the known C_2-symmetric pyrrolidine derivatives **17a**[17] and **17b**.[16b,18] Both are readily available in enantiomerically pure form from L-tartaric acid *via* a short sequence of steps. The *N*-benzylamines **17a/17b** can be converted into *o*-aminobenzamide derivatives **18a/18b**, respectively, in two steps in good overall yields by hydrogenation followed by the isatoic anhydride procedure (Scheme 4). Application of the above amide oxidation methodology to **18a/18b** provided the desired α-methoxybenzamides **19a/19b**, respectively. Due to the homotopicity of the methylene carbons flanking the nitrogen in **18a/18b** because of the C_2-symmetry of the system, it is of no significance which methylene group is oxidized.

It was our intention at this stage to effect a stereoselective chelation-controlled addition of (*p*-methoxybenzyl)magnesium chloride to **19a/b** via the corresponding *N*-acyliminium ion **20** (Scheme 5).[19] Treatment of methyl ether series **19a** with excess Grignard reagent[20]

Scheme 4



Scheme 5

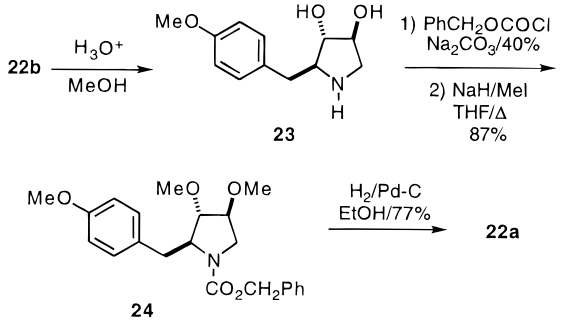


in refluxing ether afforded an excellent yield of a 1/18 mixture of alkylated pyrrolidines **21a** and **22a**. We presume that addition to an iminium complex **20** (R = Me) occurs first and that the *N*-benzoyl group contained in the initial product is removed by excess organometallic. However, the major product of the addition was shown to be the undesired *anti* compound **22a** by comparison of its spectral and optical rotation data with that previously reported.[21]

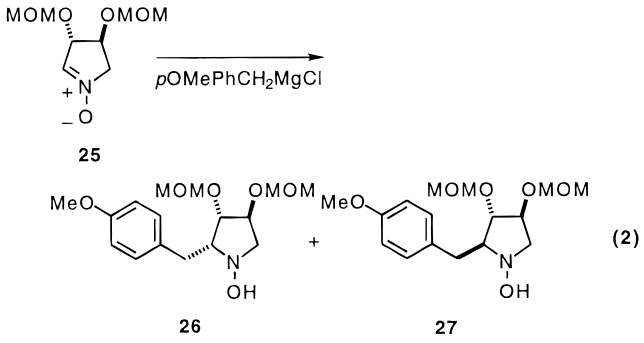
With the hope that a MOM protecting group would be a more effective *syn*-director than methyl, α-methoxybenzamide **19b** was treated with excess Grignard reagent under identical conditions. In this case a high yield of a 1/65 mixture of **21b/22b** was obtained, with the undesired *anti* isomer being formed in even greater proportion than in the methyl ether series. Since this result was rather unexpected, and because we had available only tiny amounts of the known *syn* isomer,[16b] it was decided to chemically correlate the previously unknown *anti* isomer **22b** with the methyl-protected series in order to unambiguously establish stereochemistry. Therefore, pyrrolidine **22b** was hydrolyzed using the procedure described for the *syn* isomer to yield diol **23**[22] (Scheme 6). This compound was then converted to the benzyl carbamate and *O*-dimethylated, yielding diether **24**. Finally, carbamate removal yielded pyrrolidine **22a** identical to an authentic sample.[21]

(13) Wong, C. M. *Can. J. Chem.* **1968**, *46*, 1101 and references cited therein.
(14) Sobin, B. A.; Tanner, F. W., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 4053.
(15) Korzybski, T.; Kowszyk-Gindifer, Z.; Kurytowiicz, W. *Antibiotics*; American Society of Microbiology: Washington, D.C. **1978**; Vol. 1, p 343.
(16) For lead references, see: (a) Tokuda, M.; Fujita, H.; Miyamoto, T.; Suginome, H. *Tetrahedron* **1993**, *49*, 2413. (b) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316. (c) Shi, Z.-C.; Lin, G.-Q. *Tetrahedron:Asymmetry* **1995**, *6*, 2907. (d) Yoda, H.; Nakajima, T.; Yamazaki, H.; Takabe, K. *Heterocycles* **1995**, *41*, 2423. (e) Kang, S. H.; Choi, H. *J. Chem. Soc., Chem. Commun.* **1996**, 1521.
(17) Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dorr, H.; Du Preez, N. P.; Ehrig, V.; Langer, W.; Nussler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301.
(18) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* 1986, *51*, 1069. Cicchi, S.; Hold, I.; Brandi, A. *Ibid.* **1993**, *58*, 5274.
(19) Kleinman, E. F.; Volkmann, R. A. Reactions of Allyl and Propargyl/Allenic Organometallics with Imines and Iminium Ions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 975.
(20) Treatment of α-methoxybenzamides **19a/b** with approximately 1 equiv of Grignard reagent gave no reaction.
(21) Felner, I.; Schenker, K. *Helv. Chim. Acta* **1970**, *53*, 754.
(22) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1969**, *17*, 1405.

Scheme 6



Recently, Petrini and co-workers[16b,23] reported that the closely related cyclic nitrone **25** reacts with (*p*-methoxybenzyl)magnesium chloride to afford a 2/3 mixture of *syn*/*anti* adducts **26** and **27** (eq 2). However, in the presence of $MgBr_2$ etherate in CH_2Cl_2 the selectivity reversed, now giving a 7/3 mixture of **26/27.** When we

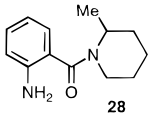


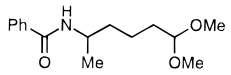
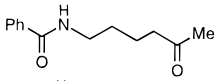
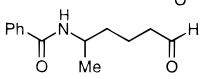
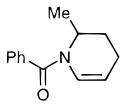
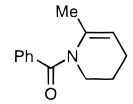
conducted the Grignard addition to α-methoxybenzamide **19a** in the presence of $MgBr_2$ etherate, a 1/12 mixture of *syn*/*anti* adducts **21a/22a** was formed, but in only 42% yield. Similar Grignard addition to MOM-protected system **19b** led to a 1/8 mixture of *syn*/*anti* products **21b/22b**, again in a poor 32% yield. Thus, although the proportions of the desired *syn* products increased somewhat, overall product yields were disappointingly low. As a result of these experiments, we have not pursued this route to anisomycin.

B. Unsymmetrical Systems. Since the scope and utility of this new methodology would be greatly expanded if the procedure showed good regioselectivity with unsymmetrical systems, we decided to next survey the amide oxidation chemistry in a series of 2-substituted piperidine derivatives. Therefore, *N*-acylation of 2-methylpiperidine was effected with isatoic anhydride to afford *o*-aminobenzamide **28**. Using our standard reaction conditions, oxidations were conducted with amide **28** at a number of temperatures to produce mixtures of products **29**−**33** (Table 2). The initially formed α-methoxybenzamides in this study, as well as those in some of the cases discussed below, are transformed *in situ* to a variety of related products, and no attempts were made to maximize the formation of any particular type of functionalized product. As can be seen from Table 2, the total isolated yield of products, as well as a low 2/1 methylene/methine regioselectivity for the reaction of **28**, remains essentially constant at all temperatures (*vide infra*). Only minor variations of the ratios of the products **29**−**33** were seen.

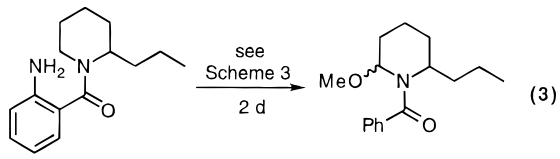
(23) See also Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706.

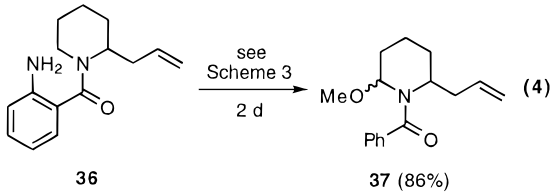
Table 2. Products of Oxidation of the *o*-Aminobenzamide of 2-Methylpiperidine



Reaction Temperature		rt	0 °C	-30 °C	-78/-60 °C
Reaction time		5 min	2 h	2 h	4 h/overnight
29		4%	0%	0%	0%
30		22%	19%	17%	19%
31		0%	12%	16%	9%
32		51%	51%	40%	53%
33		3%	7%	8%	10%
total yield		80%	89%	81%	91%
Ratio (methylene/methine)		2.2	2.4	2.2	2.1

Piperidine derivatives with larger substituents at *C*-2 were then examined to see if the regioselectivity could be improved. Thus, the 2-propyl and 2-allyl systems **34** and **36**, respectively, were oxidized (eqs 3, 4). In each case, the transformation was highly regioselective and only the products from methylene hydrogen atom transfer were isolated (*cf.* Scheme 2).

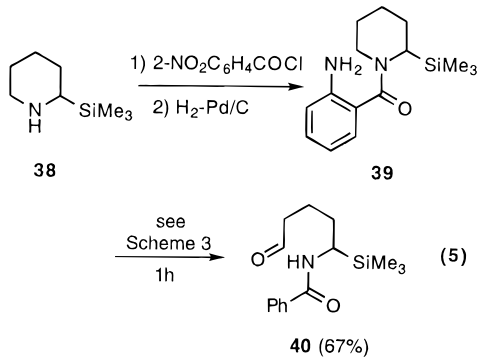




A substrate derived from 2-(trimethylsilyl)piperidine (**38**)[24] (eq 5) was also studied. In this particular example it proved more efficient to prepare the *o*-aminobenzamide **39** *via* a two-step procedure using 2-nitrobenzoyl chloride for the initial *N*-acylation, followed by nitro group reduction. Oxidation of *o*-aminobenzamide **39** once again only led to product **40** resulting from methylene hydrogen atom migration.

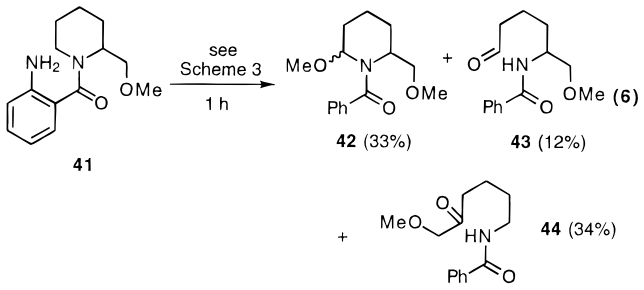
One additional piperidine derivative which was examined was 2-methoxymethyl compound **41**. Exposure of

(24) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.



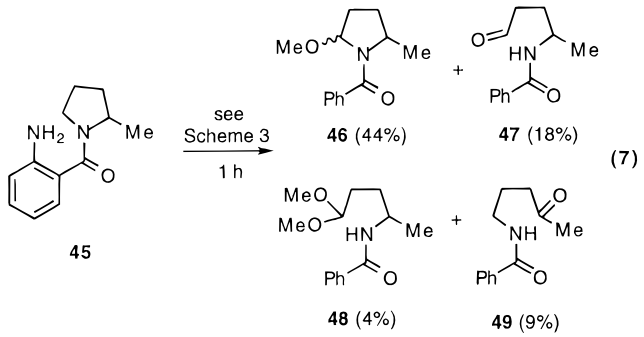
(5)

this *o*-aminobenzamide to our standard conditions afforded a mixture of oxidation products **42**−**44** (eq 6). In this case, the methylene/methine ratio is only 1.3/1, a low regioselectivity which was rather surprising (*vide infra*).

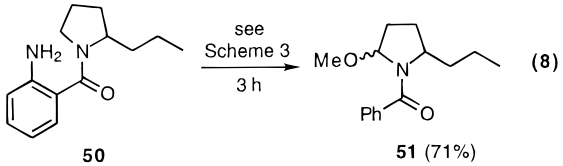


(6)

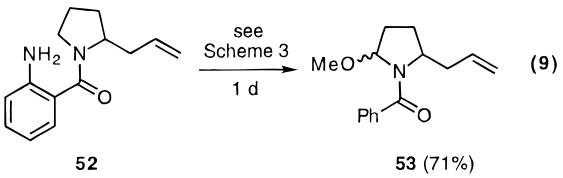
We have also examined an analogous series of unsymmetrical 2-substituted pyrrolidines. Thus, the amide **45** derived from 2-methylpyrrolidine upon oxidation produced a mixture of **46**−**49** in the isolated yields shown in eq 7. The regioselectivity with **45** is better than that



(7)



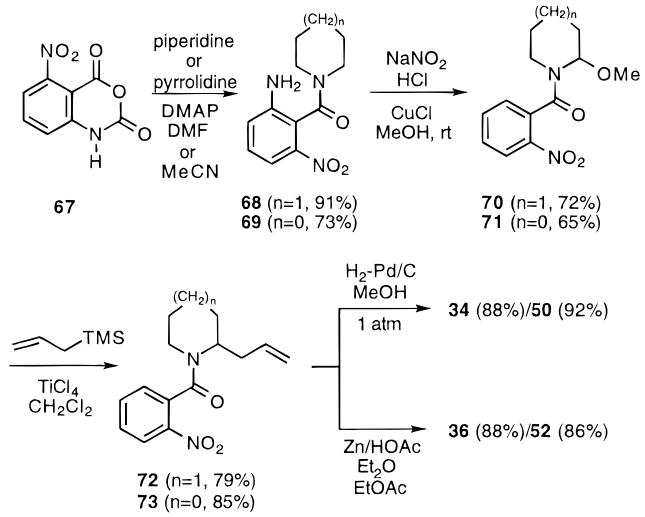
(8)



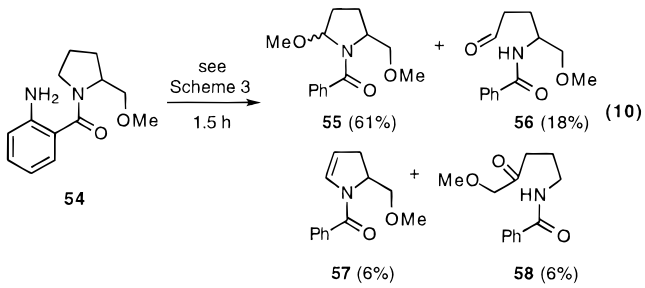
(9)

found for the 2-methylpiperidine compound **28** (7.3/1 *vs* 2.2/1, methylene/methine). In addition, the propyl- and allyl-substituted systems **50** and **52**, respectively, have been studied. In both cases, only the α-methoxybenzamides **51** and **53** derived from methylene hydrogen atom transfer could be isolated (eqs 8, 9).

Scheme 7



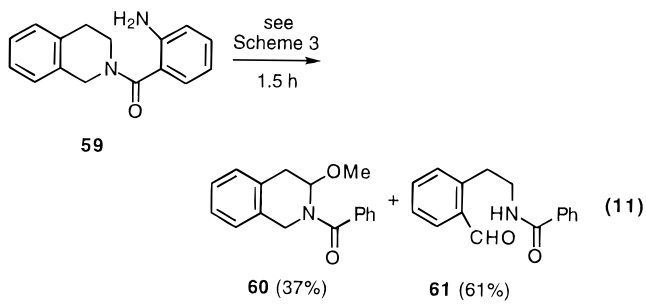
The pyrrolidine analogue **54** of 2-(methoxymethyl)-piperidine derivative **41** showed much greater regioselectivity. Therefore, oxidation of *o*-aminobenzamide **54** afforded products **55**−**58** in the isolated yields indicated (eq 10). The ratio of methylene/methine oxidation in this substrate is thus 14.2/1 (*vs* 1.3/1 for **41**).



(10)

Although the regioselectivity in the piperidine and pyrrolidine examples described here are somewhat variable, in most cases the process shows very good selectivity comparable to that of the Shono electrochemical oxidation. These studies indicate that the methodology has significant synthetic potential in the oxidation of unsymmetrical systems.

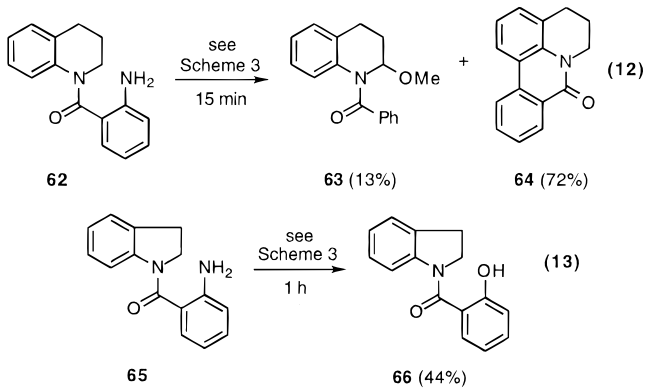
Three additional examples of unsymmetrical amide substrates have been investigated. The tetrahydroisoquinoline-derived compound **59** was oxidized to yield a mixture of **60** and **61** (eq 11). There appears to be a slight preference here for benzyl methylene hydrogen atom transfer (ratio 1.7/1). The tetrahydroquinoline *o*-amino-



(11)

benzamide **62**[25] yielded a small amount of the desired α-methoxyamide **63**, but the Pschorr cyclization product

64[26] was produced in a major amount (eq 12). Finally, the indoline system **65** led only to phenol **66** (eq 13).



C. Sequential Amide Oxidations. As a further extension of the methodology, we have examined the feasibility of conducting a series of two sequential oxidations. Commercially available 5-nitroisatoic anhydride (**67**), which is the reagent used for this purpose, was converted to the 2-amino-6-nitrobenzamides **68** and **69** with piperidine and pyrrolidine, respectively (Scheme 7). Exposure of these compounds to the standard oxidation conditions led to good yields of the α-methoxy *o*-nitrobenzamides **70** and **71**. These α-alkoxy amides could be efficiently alkylated with allyltrimethylsilane in the presence of titanium tetrachloride to afford **72** and **73**.[7,8] Both the olefin and nitro groups in **72/73** were then reduced by catalytic hydrogenation to yield 2-propyl *o*-aminobenzamides **34/50**. Also, selective reduction of the nitro functionality in **72/73** could be effected with zinc dust to give 2-allyl *o*-aminobenzamides **36/52**. As described above in eqs 3, 4, 8, and 9, substrates **34**, **50**, **36,** and **52** all undergo subsequent regioselective oxidations to afford the corresponding α-methoxybenzamides.

D. Mechanistic Discussion. In recent years, numerous examples of the synthetic uses of 1,5-hydrogen atom transfers in radical reactions have appeared.[27] Most commonly these so called "radical-translocation" reactions[27b] involve subsequent trapping of the newly formed carbon-centered radical either inter- or intramolecularly by species such as olefins or chain transfer reagents. A possible alternative fate for the translocated radical is reduction to a carbanion, and an example of this process has recently appeared.[28] The chemistry described above involves a third alternative, *i.e.* oxidation of the translocated radical to a carbonium ion.

The primary question which arises in the work outlined here is the origin of the regioselectivity in the oxidations of unsymmetrical *o*-aminobenzamides. In the Cohen studies[5] of the Hey/Turpin amide dealkylation reaction,[4]

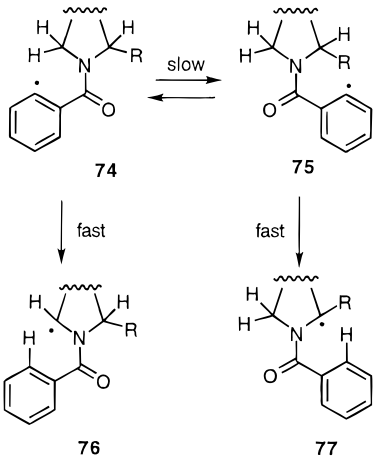
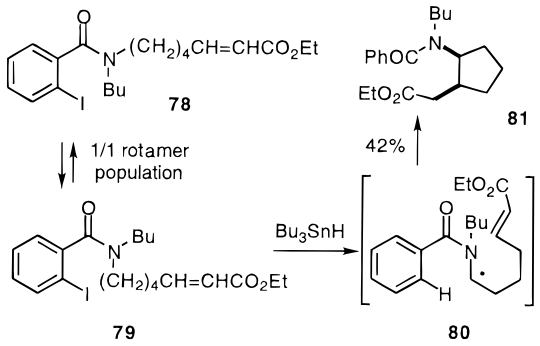


Figure 1.

Scheme 8



it was postulated based upon deuterium labeling studies that amide rotation between radicals **74** and **75** is slow relative to 1,5-hydrogen atom transfer producing α-amidyl radicals **76** and **77**, respectively (Figure 1). Later work by Grimshaw *et al.* confirmed this hypothesis.[29] In addition, more recently obtained rate data on amide rotation[30] and aryl radical lifetimes[31] support these conclusions.

The synthetic consequences of the process outlined in Figure 1 is nicely exemplified by work reported by Snieckus, Curran, and co-workers.[27a,b] For example, it was found that rotamer populations of *o*-iodobenzamides such as **78** and **79** (Scheme 8), as determined by NMR, correlate well with yields of radical cyclization products like **81**. Thus, radical **80** derived from rotamer **79** leads to the cyclization product **81**, whereas the translocated radical produced from amide rotamer **78** leads to a complex, unidentifiable mixture of products.[27b]

We believe that the regiochemistry in our amide oxidation protocol is probably also determined by rotamer populations. Examination of the *o*-aminobenzamide of 2-(methoxymethyl)piperidine (**41**) was undertaken by X-ray crystallography since this particular substrate led to apparently anomalous regiochemical results upon oxidation (*vide supra*). The structure and conformation of this amide is shown in the ORTEP plot in Figure 2.[32]

(25) *o*-Aminobenzamides **62** and **65** were prepared from the corresponding amines using the two-step *N*-acylation/NO_2-reduction procedure described for 2-(trimethylsilyl)piperidine (**38**) (eq 5).[26]

(26) Nagarajan, K.; Pillai, P. M.; Bhute, R. S. *Indian J. Chem.* **1969**, *7*, 848.

(27) (a) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896. (b) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377. (c) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343. (d) Denenmark, D.; Hoffmann, P.; Winkler, T.; Waldner, A.; De Mesmaeker, A. *Synlett* **1991**, 621. (e) Undheim, K.; Williams, L. *J. Chem. Soc., Chem. Commun.* **1994**, 883. (f) Beaulieu, F.; Arora, J.; Veith, U.; Taylor, N. J.; Chapell, B. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 8727, and references cited therein.

(28) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992**, *57*, 793.

(29) Grimshaw, J.; Haslett, R. J.; Trocha-Grimshaw, J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2448.

(30) See for example: Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517. Oki, M. *Top. Stereochem.* **1983**, *14*, 1.

(31) Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609.

(32) The authors have deposited X-ray data with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

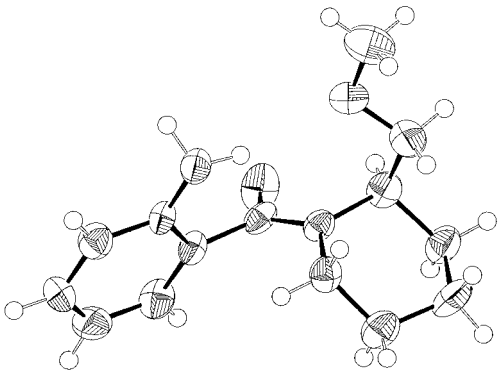


Figure 2. ORTEP plot of o-aminobenzamide **41**.

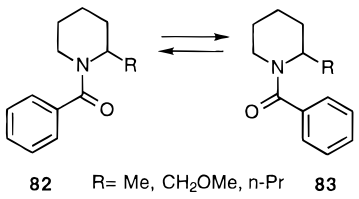
Interestingly, there is no hydrogen bonding between the amide carbonyl oxygen and the *o*-amino group, which are in an *anti* relationship. The amide rotamer found here would lead exclusively to methylene hydrogen atom abstraction rather than the 1.3/1 methylene/methine ratio observed. However, there are a number of intermediates between the *o*-aminobenzamide starting material **41** and the aryl radical and there is no simple way of knowing which radical precursor determines the final rotamer population. Thus *o*-aminobenzamide substrate conformation may in fact have no relationship to the oxidation regiochemistry.

We also examined the simple *N*-benzoyl derivatives of the three 2-substituted piperidines shown in Figure 3 since amide oxidation of the corresponding *o*-aminobenzamides of these amines give varying regioselectivities (*vide supra*). However, proton NMR analysis of the benzamides **82/83** in CD_3OD at temperatures from −50 °C to 0 °C showed 1/1 amide rotamer populations in all cases. Therefore, it appears that these unsubstituted benzamides are probably not good model systems to investigate what is occurring in the oxidation process. It might also be noted that *ortho*-substituted benzamide rotamer populations do not appear to be temperature dependent,[33] and therefore the invariance of the oxidation of the 2-methylpiperidine derivative **28** to reaction temperature is not surprising (Table 2).

From inspection of our results, it would appear that in the unsymmetrical piperidine and pyrrolidine oxidations the larger the C-2 substituent the greater the tendency for methylene *vs* methine 1,5-hydrogen atom transfer, perhaps as a result of a steric bias for rotamer **74** over **75** (Figure 1). However, the fact that the 2-(methoxymethyl)piperidine derivative **41** shows virtually no regioselectivity is not in accord with this supposition. A possible alternative explanation for this one seemingly odd result is that there may be some type of copper chelation with **41**, thus altering the regiochemical results compared to the sterically similar compounds **34** and **36**.

In an attempt to test this hypothesis, we explored the possibility of using a different metal as the oxidation catalyst. It was found that $RuCl_2(PPh_3)_3$ functions as an effective catalyst in quantities similar to CuCl, producing comparable yields of oxidation products. Interestingly, oxidation of 2-(methoxymethyl)piperidine system **41** using the ruthenium complex gave a slightly reversed regioselectivity with a methine/methylene ratio of 1.2/1 (*vs* 1.3/1 methylene/methine for CuCl). As a control, the

(33) Lewin, A. H.; Frucht, M. *Org. Magn. Reson.* **1975**, *7*, 206.



82 R= Me, CH_2OMe, n-Pr **83**

Figure 3.

2-methylpiperidine **28** was examined. Compound **28** showed a 1.9/1 methylene/methine ratio with the ruthenium catalyst (*vs* 2.2/1 with CuCl). Simlarly, 2-(methoxymethyl)pyrrolidine **54**, which gave a 14.2 methylene/methine selectivity with copper, showed a reduced 11/1 selectivity with the ruthenium catalyst. As a control here, 2-methylpyrrolidine **45** showed a 4.7/1 methylene/methine regioselectivity with ruthenium (*vs* 7.3/1 with CuCl). Thus there seems to be a loss in methylene selectivity in all four cases examined using catalytic ruthenium, but since these changes are rather small, we are uncertain at present as to the significance of these results, and to whether there is any effect of the metal other than acting as a redox reagent.

Conclusion

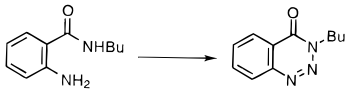
An efficient two-step preparative method has been developed for converting a secondary amine[34] to an α-methoxybenzamide. The methodology shows good regioselectivity with many unsymmetrical α-substituted pyrrolidines and piperidines, although further studies are needed to more fully delineate the mechanistic origin of this selectivity. We are continuing to investigate the scope and limitations of the chemistry outlined here and are applying the protocol to alkaloid total synthesis.[11b]

Experimental Section

General. Chemicals were purchased from Aldrich Chemical Co. except for 5-nitroisatoic anhydride and 2-methylpyrrolidine which were obtained from Pfaltz and Bauer, and Alfa, respectively. Reactions were run under an atmosphere of argon. Flash chromatography was performed using EM Sciences silica gel 60. Preparative TLC was done with EM silica gel 60 PF_{254}. Melting points are uncorrected. Combustion analyses were carried out by Atlantic Microlab.

General Procedure for Synthesis of *o*-Aminobenzamides. To a solution of isatoic anhydride (**12**, ∼30 mmol) (or 5-nitroisatoic anhydride (**67**)) in DMF (0.5 M solution) was added the amine (1.1 equiv) in the presence of DMAP (0.1 equiv) at 0 °C. After 2−3 h at 0 °C the reaction mixture was warmed to rt, stirred for 20−24 h, diluted with water (100 mL), and extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with brine (50 mL × 2), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/hexanes, 1/1−2/1). Compounds **14a**−**c** and **14f** have been previously prepared.[12]

(34) Application of the procedure to the *o*-aminobenzamide **i** derived from a primary amine led to heterocycle **ii** in 98% yield.[35]



i **ii**

(35) *cf.* LeBlanc, R. J.; Vaughn, K. *Can. J. Chem.* **1972**, *50*, 2544. Hasspacher, K.; Ohnacker, G. US Patent 3,316,262 (*Chem. Abstr.* **1967**, *67*, 64445q).

14d (mixture of diastereomers, colorless oil, 98%): IR (neat) 3445, 3351, 1634 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.17 (dt, J = 7.9, 1.4 Hz, 1H), 7.05 (dt, J = 7.9, 1.4 Hz, 1H), 6.75−6.70 (m, 2H), 4.29 (rotamers, br s, 3H), 4.02 (br s, 1H), 3.57−3.50 (rotamers, m, 2H), 2.62 (br t, 2H), 1.11 (d, J = 6.1 Hz, 6H); EIMS m/z (relative intensity) 234 (M^+, 19), 120 (o-NH_2PhCO^+, 100); HRMS ($C_{13}H_{18}N_2O_2$) calcd 234.1368, found 234.1366.

14e (white solid, 85%): mp 72−73.5 °C; IR (film) 3470, 3383, 1626 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.18−7.06 (m, 2H), 6.74−6.66 (m, 2H), 4.14 (br s, 2H), 3.62 (br s, 2H), 3.39 (br s, 2H), 1.95−1.36 (m, 8H); EIMS m/z (relative intensity) 218 (M^+, 34), 120 (o-NH_2PhCO^+, 100); HRMS ($C_{13}H_{18}N_2O$) calcd 218.1419, found 218.1414.

2-Methylpiperidine *o*-aminobenzamide (28) (white solid, 49%): mp 91−94 °C; ^1H NMR (200 MHz/$CDCl_3$) δ 7.14 (d, J = 7.2 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.74−6.67 (m, 2H), 4.55 (rotamers, br s, 1H), 4.15 (br s, 2H), 4.07 (rotamers, br s, 1H), 2.95 (rotamers, t, J = 13.1 Hz, 1H), 1.65−1.43 (m, 6H), 1.18 (d, J = 6.9 Hz, 3H). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.84. Found: C, 71.40; H, 8.29; N, 12.77.

2-(Methoxymethyl)piperidine *o*-aminobenzamide (41) (white solid, 67%): recrystallized from Et_2O/hexanes, mp 106−107 °C; ^1H NMR (200 MHz/$CDCl_3$) δ 7.20−7.05 (m, 2H), 6.73−6.61 (m, 2H), 4.32 (br s, 2H), 3.72 (t, J = 14 Hz, 2H), 3.45−3.20 (m, 4H), 3.15−2.90 (m, 2H), 1.70−1.45 (m, 6H); CIMS m/z (relative intensity) 249 (MH^+, 100), 217 (M^+ − OMe, 5), 203 (M^+ − C_2H_5O, 40), 120 (o-NH_2PhCO^+, 70).

2-Methylpyrrolidine *o*-aminobenzamide (45) (tan solid, 68%): mp 79−82 °C; IR ($CDCl_3$) 1614 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.18−7.09 (m, 2H), 6.70−6.64 (m, 2H), 4.54 (br s, 2H), 4.26 (br s, 1H), 3.48 (br s, 2H), 2.13−1.49 (m, 3H), 1.23−1.16 (m, 4H); EIMS m/z (relative intensity) 204 (M^+, 28), 120 (o-NH_2PhCO^+, 100), 84 ($C_5H_{10}N$, 54); HRMS ($C_{12}H_{16}N_2O$) calcd 204.1263, found 204.1267.

2-(Methoxymethyl)pyrrolidine *o*-aminobenzamide (54) (colorless oil, 82%): IR (CCl_4) 3476, 3366, 1628 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.22−7.10 (m, 2H), 6.72−6.65 (m, 2H), 4.49 (br s, 2H), 4.38 (br s, 2H), 3.47−3.32 (m, 3H), 2.06−1.81 (m, 4H); CIMS m/z (relative intensity) 235 (MH^+, 100).

Tetrahydroisoquinoline *o*-aminobenzamide (59) (light yellow oil, 98%): IR (neat) 3454, 3353, 1614 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.22−7.06 (m, 6H), 6.78−6.69 (m, 2H), 4.76 (br s, 2H), 4.36 (br s, 2H), 3.79 (br s, 2H), 2.89 (t, J = 6.1 Hz, 2H); CIMS m/z (relative intensity) 253 (MH^+, 100); EIMS m/z (relative intensity) 252 (M^+) HRMS ($C_{16}H_{16}N_2O$) calcd 252.1263, found 252.1262.

Piperidine 2-amino-6-nitrobenzamide (68) (yellow solid, 91%): (from 5-nitroisatoic anhydride): recrystallized from benzene/hexanes, mp 163−164 °C; IR (CH_2Cl_2) 3495, 3377, 1619, 1325 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 8.10−8.06 (m, 2H), 6.70 (dd, J = 9.5, 2.0 Hz, 1H), 5.21 (br s, 2H), 3.56 (br s, 4H), 1.65−1.58 (m, 6H); CIMS m/z (relative intensity) 250 (MH^+, 100). Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.90; H, 6.09; N, 16.93.

Pyrrolidine 2-amino-6-nitrobenzamide (69) (tan solid, 73%): (from 5-nitroisatoic anhydride, CH_3CN was used as solvent): recrystallized from ethyl acetate/hexanes, mp 215−216 °C; ^1H NMR (200 MHz/$CDCl_3$) δ 8.24 (d, J = 2.6 Hz, 1H), 8.06 (dd, J = 9.1, 2.6 Hz, 1H) 6.67 (d, J = 9.1 Hz, 1H), 5.64 (br s, 2H), 3.60 (br s, 4H), 1.94 (br s, 4H); CIMS m/z (relative intensity) 236 (MH^+, 100), 165 (M^+ − C_4H_8N, 5). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.26; H, 5.58; N, 17.95.

Standard Conditions for Synthesis of α-Methoxybenzamides. To a solution of the *o*-aminobenzamide (1−3 mmol) in MeOH (0.05 M solution) was added $NaNO_2$ (2 equiv) and CuCl (5 mol %). Methanolic HCl (3%, 3 equiv) was added over 5−10 min, and the reaction mixture was stirred at rt for the time indicated. The reaction mixture was diluted with saturated $NaHCO_3$ solution, and methanol was removed by rotary evaporation. The residue was extracted with ethyl acetate (30 mL × 3), washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative TLC (ethyl acetate/hexanes, 1/2−1/1).

α-Methoxybenzamide 15a (colorless oil; 43%), slightly modified conditions were used: $NaNO_2$ (3 equiv), HCl (3.3 equiv), CuCl (2 mol%) (1.5 h): (IR (film) 1650 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.55−7.34 (m, 5H), 5.72 and 4.66 (rotamers, br s, 1H), 3.61 and 3.22 (rotamers, br t, 2H), 3.40 and 2.97 (rotamers, 2s, 3H), 2.16−1.52 (m, 4H); EIMS m/z (relative intensity) 205 (M^+, 2), 105 (100), 77 (40); HRMS ($C_{12}H_{15}NO_2$) calcd 205.1103, found 205.1088.

Amido acetal 15a′ (pale yellow oil; 82%) (2 d): IR (film) 3326, 1643 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.76 (dd, J = 7.7, 1.9 Hz, 2H), 7.49−7.38 (m, 3H), 6.45 (br s, 1H), 4.38 (t, J = 5.1 Hz, 1H), 3.44 (q, J = 2.9 Hz, 2H), 3.30 (s, 6H), 1.69−1.04 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 167.2, 130.8, 129.8, 128.0, 126.7, 104.1, 52.6, 39.4, 29.7, 24.1; CIMS m/z (relative intensity) 238 (MH^+, 6), 206 (M^+ − OMe, 100), 105 ($PhCO^+$, 51); HRMS ($C_{13}H_{18}NO_3$) calcd 236.1287, found 236.1273.

α-Methoxybenzamide 15b (colorless oil; 69%) (1.5 h): IR (film) 1644 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.40 (m, 5H), 6.40 and 4.86 (rotamers, br s, 1H), 3.39 and 3.06 (rotamers, br s, 3H), 3.24 and 2.97 (rotamers, br t, 2H), 1.36−2.00 (m, 6H); CIMS m/z (relative intensity) 220 (MH^+, 8), 188 (M^+ − OMe, 100), 105 ($PhCO^+$, 45); HRMS ($C_{13}H_{17}NO_2$) calcd 219.1259, found 219.1260.

Amido acetal 15b′ (colorless oil, 49%) (3 d): IR (film) 3324, 1634 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$) δ 7.72 (dd, J = 7.0, 1.6 Hz, 2H), 7.38−7.25 (m, 3H), 7.04 (br s, 1H), 4.24 (t, J = 5.6 Hz, 1H), 3.28 (q, J = 7.0 Hz, 2H), 3.21 (s, 6H), 1.55−1.46 (m, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 167.2, 130.7, 129.8, 127.9, 126.7, 104.1, 52.3, 39.5, 31.8, 28.9, 21.6; CIMS m/z (relative intensity) 252 (MH^+, 7), 220 (M^+ − OMe, 100), 105 ($PhCO^+$, 15); HRMS ($C_{14}H_{20}NO_3$) calcd 250.1443 (M^+ − H), found 250.1459.

α-Methoxybenzamide 15c (light yellow oil, 68%) (27 h): IR (film) 1644 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.44 (m, 5H), 5.70 and 4.70 (rotamers, br s, 1H), 3.57 and 3.54 (rotamers, s, 3H), 4.30−3.04 (m, 6H); EIMS m/z (relative intensity) 221 (M^+, 7), 190 (M^+ − OMe, 8), 116 (M^+ − PhCO, 9), 105 ($PhCO^+$, 100); HRMS ($C_{12}H_{15}NO_3$) calcd 221.1052, found 221.1048.

α-Methoxybenzamide 15d (light yellow oil, 71%) (3 d): IR ($CDCl_3$) 1633 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.40 (m, 5H), 5.50 and 4.47 (rotamers, s, 1H), 4.43 and 3.14 (rotamers, d, J = 2.1 Hz, 1H), 3.70 and 3.54 (rotamers, m, 2H), 3.53 and 3.06 (rotamers, two s, 3H), 3.26 and 2.84 (rotamers, t, J = 2.1 Hz, 1H), 1.35 (t, J = 5.6 Hz, 3H), 1.12 and 1.05 (rotamers, d, J = 5.6 Hz, 3H); EIMS m/z (relative intensity) 249 (M^+, 8), 218 (M^+ − OMe, 2), 144 (M^+ − PhCO, 12), 105 ($PhCO^+$, 100); HRMS ($C_{14}H_{19}NO_3$) calcd 249.1365, found 249.1366.

α-Methoxybenzamide 15e (pale yellow solid, 73%): mp 57−59 °C (2 h): IR ($CDCl_3$) 1626 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.47−7.34 (m, 5H), 5.94 and 4.83 (rotamers, t, J = 7.1 Hz, 1H), 4.24 (dt, J = 13.7, 3.3 Hz, 1H), 3.38 and 3.03 (rotamers, s, 3H), 2.28−2.14 (m, 1H), 1.92−1.35 (m, 8H); CIMS m/z (relative intensity) 234 (MH^+, 16), 202 (M^+ − OMe, 81), 128 (M^+ − PhCO, 17), 105 ($PhCO^+$, 100); HRMS ($C_{14}H_{19}NO_2$) calcd 233.1416, found 233.1413.

α-Methoxybenzamide 15f (yellow oil, 86%), 4 Å molecular sieves were used (1 h): ^1H NMR (300 MHz/$CDCl_3$) δ 7.38−7.27 (m, 5H), 4.82 and 3.65 (rotamers, 2bs, 1H), 3.35−3.26 (m, 2H), 3.04 (br s, 3H) 1.40−1.38 (d, J = 6.0 Hz, 3H), 1.32−1.27 (m, 3H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.8, 136.8, 129.4, 128.5, 126.6, 86.3, 54.5, 34.1, 20.1, 14.3; CIMS m/z (relative intensity) 208 (MH^+, 20), 176 (M^+ − OMe, 100), 105 ($PhCO^+$, 20).

Amido acetal 29 (yellow oil): ^1H NMR (300 MHz/$CDCl_3$) δ 7.75 (d, J = 7.7 Hz, 2H), 7.52−7.36 (m, 3H), 5.96 (br d, J = 7.7 Hz, 1H), 4.32 (t, J = 5.5 Hz, 1H), 4.26−4.13 (m, 1H), 3.27 (s, 6H), 1.59−1.36 (m, 6H), 1.19 (d, J = 6.7 Hz, 3H); EIMS m/z (relative intensity) 234 (M^+ − OMe, 4), 105 ($PhCO^+$, 100).

Amido ketone 30 (light yellow solid): mp 72−73.5 °C; IR ($CDCl_3$) 1714, 1655 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$) δ 7.79 (dd, J = 7.9, 1.4 Hz, 2H), 7.52−7.40 (m, 3H), 6.38 (br s, 1H), 3.45 (q, J = 6.5 Hz, 2H), 2.52 (t, J = 6.5 Hz, 2H), 2.16 (s, 3H), 1.73−1.61 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 167.4, 134.6, 131.2, 128.3, 126.8, 42.8, 39.4, 29.9, 28.7, 20.5; EIMS m/z (relative intensity) 219 (M^+, 5), 114 (M^+ − PhCO, 4), 105 ($PhCO^+$, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.12; H, 7.85; N, 6.47.

Amido aldehyde 31 (yellow solid): mp 76−77 °C; IR ($CDCl_3$) 1726, 1660 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 9.87 (t,

J = 1.4 Hz, 1H), 7.88 (dd, J = 7.7, 1.9 Hz, 2H), 7.56−7.47 (m, 3H), 6.34 (d, J = 7.3 Hz, 1H), 4.31−4.27 (m, 1H), 2.56 (t, J = 7.2 Hz, 2H), 1.81−1.55 (m, 4H), 1.30 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 202.3, 167.1, 134.7, 131.3, 128.5, 126.8, 45.4, 43.5, 36.2, 21.0, 18.4; EIMS m/z (relative intensity) 219 (M^+, 4), 105 ($PhCO^+$, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.13; H, 7.84; N, 6.44.

Enamide 32 (colorless oil): IR (neat) 1633 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.35 (m, 5H), 5.94 and 4.75 (rotamers, br s, 1H), 4.90 and 3.89 (rotamers, br s, 1H), 3.41 (br s, 1H), 3.01 (br s, 2H), 2.22−1.28 (m, 5H); EIMS m/z (relative intensity) 201 (M^+, 4), 105 ($PhCO^+$,100); HRMS ($C_{13}H_{15}NO$) calcd 201.1154, found 201.1164.

Enamide 33 (colorless oil): ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.57 (d, J = 6.5 Hz, 2H), 7.44 (m, 3H), 5.06 (br t, 1H), 3.62 (t, J = 5.3 Hz, 2H), 1.76−1.50 (m, 7H); EIMS m/z (relative intensity) 201 (M^+, 100), 105 ($PhCO^+$, 55).

α-Methoxybenzamide 35 (yellow oil, 71%), slightly modified conditions were used: $NaNO_2$ (2.7 equiv), HCl (15.3 equiv), CuCl (20 mol%) (2 d): IR (film) 1633 cm^{-1}; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.31−7.21 (m, 2H), 6.91−6.83 (m, 3H), 4.83, 4.50, 3.45 (rotamers, br s, 1H), 3.74 (br s, 3H), 2.98−2.79 (rotamers, two br s, 1H), 1.59−1.20 (br s, 10H), 0.87 (br s, 3H); ^{13}C NMR (75 MHz/$CDCl_3$, 50 °C) δ 159.7, 129.4, 128.9, 126.5, 118.7, 114.9, 112.2, 55.3, 32.1. 28.5, 26.1, 19.4, 19.1, 13.9; EIMS m/z (relative intensity) 261 (M^+, 21), 218 ($M^+ - C_3H_7$, 57), 135 (100); HRMS ($C_{16}H_{23}NO_2$) calcd 261.1729, found 261.1734.

α-Methoxybenzamide 37 (pale yellow oil, 86%), slightly modified conditions were used: $NaNO_2$ (2.2 equiv), HCl (6.3 equiv), CuCl (10 mol%) (2 d): IR (film) 1633 cm^{-1}); ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.38−7.22 (m, 3H), 6.90−6.86 (m, 2H), 5.72 (br s, 1H), 5.09−4.80 (m, 3H), 3.76 (br s, 3H), 2.93 (br s, 1H), 2.50−2.35 and 2.35−2.15 (rotamers, 2m, 2H), 1.59 (br s, 6H); CIMS m/z (relative intensity) 260 (MH^+,100), 218 ($M^+ - C_3H_5$, 42), 105 ($PhCO^+$, 10); HRMS ($C_{16}H_{21}NO_2$) calcd 259.1572, found 259.1567.

Amido aldehyde 40 (yellow oil, 67%) (1 h): IR ($CDCl_3$) 3437, 1724, 1652 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 9.79 (s, 1H), 7.78−7.73 (m, 2H), 7.51−7.41 (m, 3H), 5.85 (br d, J = 10 Hz, 1H), 3.80−3.45 (m, 1H), 2.53−2.41 (m, 2H), 1.79−1.41 (m, 4H), 0.023 (s, 9H); CIMS m/z 278 (MH^+, 100), 262 ($M^+ -$ Me, 20), 249 ($M^+ - CHO^+$, 20), 105 ($PhCO^+$, 10); HRMS ($C_{15}H_{23}N_2OSi$) calcd 277.1498, found 277.1479.

α-Methoxybenzamide 42 (colorless oil, 33%), slightly modified conditions were used: $NaNO_2$ (2.1 equiv), HCl (9.1 equiv), CuCl (18 mol%) (1 h): IR (film) 1644 cm^{-1}; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.39 (s, 5H), 5.91, 4.86 (rotamers, br s, 1H), 3.95, 3.75 (rotamers, m, 1H), 3.59−3.53 (m, 2H), 3.46−3.37 (m, 3H), 3.18 (br s, 1H), 3.01 (br s, 2H), 2.04−1.85 (m, 3H), 1.76−1.50 (m, 3H); CIMS m/z (relative intensity) 264 (MH^+, 5), 232 ($M^+ -$ OMe, 100), 218 ($M^+ - C_2H_5O$, 5), 105 ($PhCO^+$, 10); HRMS ($C_{15}H_{21}NO_3$) calcd 263.1521, found 263.1518.

Amido aldehyde 43 (yellow oil, 12%): IR (neat) 3507, 3319, 2932, 1722, 1640 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 9.76 (t, J = 1 Hz, 1H), 7.81−7.73 (m, 2H), 7.52−7.48 (m, 3H), 6.46 (m, 1H), 4.29 (m, 1H), 3.50 (t, J = 2 Hz, 2H), 3.36 (s, 3H), 2.57−2.49 (m, 2H), 1.80−1.51 (m, 4H); EIMS m/z (relative intensity) 249 (M^+, 7), 218 ($M^+ -$ OMe, 10), 204 ($M^+ - C_2H_5O$, 12), 105 ($PhCO^+$, 100).

Amido ketone 44 (yellow oil, 34%): IR (neat) 3334, 3063, 2934, 1731, 1650 cm^{-1}; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.79−7.77 (m, 2H), 7.48−7.39 (m, 3H), 6.50 (br s, 1H), 4.00 (s, 2H), 3.46−3.40 (m, 5H), 2.51 (t, J = 6.7 Hz, 2H), 1.71−1.60 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 208.6, 167.5, 134.6, 131.3, 128.5, 126.8, 77.6, 59.3, 39.4, 38.0, 28.9, 20.0; EIMS m/z (relative intensity) 249 (M^+, 6), 204 ($M^+ - C_2H_5O$, 1), 105 ($PhCO^+$, 100), 77 ($C_6H_5^+$, 32); HRMS ($C_{14}H_{19}NO_3$) calcd 249.1365, found 249.1350.

α-Methoxybenzamide 46 (yellow oil, 44%) (1 h): ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.62−7.37 (m, 5H), 4.69 (br s, 1H), 4.45−4.30 and 4.15 (rotamers, m, 1H), 3.25−3.02 (br s, 2H), 2.76 (br s, 1H), 2.30−1.45 (m, 4H), 1.36−1.22 (m, 3H); CIMS m/z (relative intensity) 220 (MH^+, 20) 188 ($M^+ -$ OMe, 100), 105 ($PhCO^+$, 25) .

Amido aldehyde 47 (yellow oil, 18%): IR (neat) 3318, 1819, 1719, 1637 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 9.83 (s, 1H), 7.78−7.72 (m, 1H), 7.53−7.38 (m, 4H), 6.12 (br s, 1H), 4.30−4.00 (m, 1H), 2.56 (q, J = 6.4 Hz, 2H), 1.88 (q, J = 6.8 Hz, 2H), 1.23 (d, J = 6.6 Hz, 3H); EIMS m/z (relative intensity) 205 (M^+, 2), 105 ($PhCO^+$, 100), 77 ($C_6H_5^+$, 37).

Amido acetal 48 (yellow oil, 4%): ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.78−7.73 (m, 1H), 7.49−7.37 (m, 4H), 6.11 (br s, 1H), 4.35 (t, J = 4.8 Hz, 1H), 4.20−3.95 (m, 1H), 3.30 (d, J = 4.4 Hz, 6H), 1.70−1.50 (m, 4H), 1.21 (d, J = 6.6 Hz, 3H); CIMS m/z (relative intensity) 251 (MH^+, 2), 220 ($M^+ -$ OMe, 100), 105 ($PhCO^+$, 20).

Amido ketone 49 (yellow oil, 9%): IR (neat) 3325, 1714, 1644 cm $^{-1}$; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.80−7.77 (m, 2H), 7.53−7.41 (m, 3H), 6.57 (br s, 1H), 3.48 (q, J = 5.7 Hz, 2H), 2.62 (t, J = 6.6 Hz, 2H), 2.18 (s, 3H), 1.93 (q, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 209.4, 167.4, 134.5, 131.4, 128.6, 126.8, 41.4, 39.9, 30.1, 23.0; CIMS m/z (relative intensity) 206 (MH^+, 100), 105 ($PhCO^+$, 20).

α-Methoxybenzamide 51 (yellow oil, 71%), slightly modified conditions were used: $NaNO_2$ (2.4 equiv), HCl (7.5 equiv), CuCl (7 mol %) (3 h): IR (film) 1633 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.52−7.20 (m, 4H), 7.05−6.85 (m, 1H), 4.25 (br s, 1H), 3.76 (br s, 3H), 3.45−3.25 (m, 1H), 2.20−1.50 (m, 4H), 1.45−1.00 (m, 4H), 0.95−0.80 (m, 3H); EIMS m/z (relative intensity) 247 (M^+, 2), 174 ($M^+ - C_3H_7$, 20), 135 (100); HRMS ($C_{15}H_{21}NO_2$) calcd 247.1572, found 247.1565.

α-Methoxybenzamide 53 (yellow oil, 71%); slightly modified conditions were used: $NaNO_2$ (3.0 equiv), HCl (11.9 equiv), CuCl (5 mol %) (1 d): ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.40−7.15 (m, 1H), 7.10−6.85 (m, 4H), 6.00−5.75 (m, 1H), 5.20−4.80 (m, 2H), 4.30 (br s, 1H), 3.78 (s, 3H), 3.38 (t, J = 12 Hz, 1H), 2.75−2.55 (m, 1H), 2.50−2.25 (m, 1H), 2.00−1.65 (m, 4H); CIMS m/z (relative intensity) 246 (MH^+, 100), 204 ($M^+ -$ OMe, 30), 135 (40), 105 ($PhCO^+$, 5).

α-Methoxybenzamide 55 (colorless oil, 61%) (1.5 h): ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.63−7.39 (m, 5H), 4.78 and 4.47 (rotamers, br s, 1H), 3.57 and 3.00 (rotamers, br s, 2H), 3.37 (s, 4H), 3.15 and 2.77 (rotamers, s, 3H), 2.18−1.83 (m, 4H); EIMS m/z (relative intensity) 249 (M^+, 2), 218 ($M^+ -$ OMe, 5), 105 ($PhCO^+$, 100).

Amido aldehyde 56 (colorless oil, 18%): ^{1}H NMR (300 MHz/$CDCl_3$) δ 9.79 (br t, 1H), 7.77 (d, J = 6.8 Hz, 2H), 7.52−7.32 (m, 3H), 6.55 (br d, J = 7.9 Hz, 1H), 4.29 (m, 1H), 3.49 (d, J = 3.2 Hz, 2H), 3.36 (s, 3H), 2.14−1.89 (m, 4H); EIMS m/z (relative intensity) 235 (M^+, 1), 190 ($M^+ - C_2H_5O$, 13), 105 ($PhCO^+$, 100).

Enamide 57 (colorless oil, 6%): ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.56−7.28 (m, 5H), 4.87 and 4.43 (rotomers, br s, 1H), 3.67−3.22 (m, 4H), 3.49 (s, 3H), 2.36−2.02 (m, 2H); EIMS m/z (relative intensity) 217 (M^+, 1), 105 ($PhCO^+$, 100).

Amido ketone 58 (colorless oil, 6%): IR (film) 3314, 1725, 1642 cm^{-1}; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.77 (d, J = 7.6 Hz, 2H), 7.51−7.40 (m, 3H), 6.55 (br s, 1H), 4.24 (s, 2H), 3.48 (q, J = 6.3 Hz, 2H), 3.39 (s, 3H), 2.60 (t, J = 6.7 Hz, 2H), 1.95 (m, 2H); EIMS m/z (relative intensity) 235 (M^+, 2), 190 ($M^+ - C_2H_5O$, 10), 105 ($PhCO^+$, 100); HRMS ($C_{13}H_{17}NO_3$) calcd 235.1208, found, 235.1211.

α-Methoxybenzamide 60 (colorless oil, 37%) (1.5 h): ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.47 (s, 5H), 7.30−7.17 (m, 4H), 5.30 and 4.53 (rotamers, br s, 1H), 5.22 and 4.42 (rotamers, br d, 2H), 4.53 and 3.62 (rotamers, br s, 1H), 3.50 and 3.15 (rotamers, br s, 3H), 3.24 and 3.01 (rotamers, br d, 2H); EIMS m/z (relative intensity) 267 (M^+, 0.4), 236 ($M^+ -$ OMe, 9), 105 ($PhCO^+$, 100).

Amido aldehyde 61 (colorless oil, 61%): ^{1}H NMR (300 MHz/$CDCl_3$) δ 10.17 (s, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.44−7.35 (m, 7H), 6.84 (br s, 1H), 3.70 (q, J = 6.5 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H); EIMS m/z (relative intensity) 253 (M^+, 5), 148 ($M^+ -$ PhCO, 5), 105 ($PhCO^+$, 100).

2-Methoxytetrahydroquinoline benzamide (63) (white solid, 13%) (15 min): mp 95−98 °C; IR ($CDCl_3$) 1643 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.38−7.17 (m, 6H), 7.03 (t, J = 7.4 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.03−5.99 (m, 1H), 3.41 (s, 3H), 2.90−2.78 (m, 2H), 2.41−2.34 (m, 1H), 2.10−2.05 (m, 1H); CIMS m/z (relative intensity) 267 (M^+, 20), 236 ($M^+ -$ OMe, 100), 105 ($PhCO^+$, 50); HRMS ($C_{17}H_{17}NO_2$) calcd 267.1259, found 267.1265.

2-Methoxypiperidine *o*-nitrobenzamide (70) (yellow oil, 72%) (15 min): IR ($CDCl_3$) 1634 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 8.22−8.18 (m, 2H), 7.70−7.53 (m, 2H), 5.78, 4.67 (rotamers, br s, 1H), 4.31, 3.29, 3.01 (rotamers, br s, 5H), 1.93−1.51 (m, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 168.8, 148.0, 137.8, 132.8, 129.8, 124.5, 122.0, 85.5, 79.9 (rotamers), 55.2, 54.2 (rotamers) 43.0, 37.5 (rotamers), 30.1, 25.8, 24.8 (rotamers), 18.4; EIMS *m*/*z* (relative intensity) 264 (M^+, 9), 233 (M^+ − OMe, 17) 150 (*o*-NO_2PhCO^+, 100); HRMS ($C_{13}H_{16}N_2O_4$) calcd 264.1110, found, 264.1090.

2-Methoxypyrrolidine *o*-nitrobenzamide (71) (yellow oil, 65%) (50 min): IR ($CDCl_3$) 1636 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 8.64 (s, 1H), 8.41−8.30 (m, 1H), 8.00 (m, 1H), 7.64 (t, J = 8.0 Hz, 1H), 5.71, 4.64 (rotamers, m, 1H), 3.78−3.51 and 3.46 (rotamers, m, 2H), 3.11 (s, 3H), 2.16−1.66 (m, 4H); CIMS *m*/*z* (relative intensity) 251 (MH^+, 50), 219 (M^+ − OMe, 100), 150 (*o*-NO_2PhCO^+, 10); HRMS ($C_{14}H_{14}N_2O_4$) calcd 250.0953, found 250.0941.

Preparation of *N*-Acylpyrrolidines 18a and 18b. To a solution of the *N*-benzylpyrrolidine (**17a**, 1.54 g, 6.97 mmol; **17b**, 4.65 g, 16.55 mmol) in MeOH (for **17a**, 140 mL; for **17b**, 250 mL) was added $Pd(OH)_2$ on carbon (for **17a**, 0.3 g; for **17b**, 0.5 g). The reaction mixture was hydrogenated under 1 atm of H_2 at rt for 3 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was evaporated to give the crude amine which was used for the next step without further purification.

To a solution of isatoic anhydride (for **18a**, 1.14 g, 7.0 mmol; for **18b**, 2.7 g, 16.6 mmol) in DMF (for **18a**, 4 mL; for **18b**, 17 mL) was added the above crude pyrrolidine in DMF (3 mL) at 0 °C in the presence of DMAP (for **18a**, 84 mg; for **18b**, 0.5 g). The reaction mixture was allowed to warm to rt, stirred for 15 h, diluted with brine (10 mL), and extracted with ethyl acetate (30 mL × 3). The organic extract was washed with brine (30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (for **18a**, ethyl acetate; for **18b**, ethyl acetate/hexanes, 1/1) to give the *N*-acylpyrrolidine (**18a**, light yellow solid, recrystallized from ethyl acetate/hexanes, mp 105−106 °C, 1.2 g, 68%; **18b**, a light yellow oil, 4.4 g, 86%).

18a: ^1H NMR (200 MHz/$CDCl_3$) δ 7.24−7.05 (m, 2H), 6.75−6.55 (m, 2H), 4.68 (br s, 2H), 3.94−3.45 (m, 6H), 3.35 (br s, 6H); CIMS *m*/*z* (relative intensity) 251 (MH^+, 100), 120 (*o*-NH_2PhCO^+, 37). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.49; H, 7.25; N, 11.22.

18b: IR (film) 3456, 3355, 1621 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.22−7.05 (m, 2H), 6.71−6.58 (m, 2H), 4.65 (br s, 6H), 4.13 (br s, 2H), 3.97−3.44 (m, 4H), 3.38 (br s, 6H); CIMS *m*/*z* (relative intensity) 311 (MH^+, 100), 279 (M^+ − OMe, 19), 248 (M^+ − 2OMe, 3); HRMS ($C_{15}H_{22}N_2O_5$) calcd 310.1529, found, 310.1552.

Preparation of α-Methoxybenzamides 19a and 19b. To a solution of the amine (**18a**: 0.69 g, 2.77 mmol; **18b**: 0.35 g, 1.13 mmol) and $NaNO_2$ (for **19a**, 0.35 g, 5.54 mmol; for **19b**, 156 mg, 2.3 mmol) in MeOH (for **19a**, 50 mL; for **19b**, 22 mL) were added 3% methanolic HCl (for **19a**, 15.8 mL, 13.9 mmol; for **19b**, 3.8 mL, 3.4 mmol) and CuCl (for **19a**, 14 mg; for **19b**, 6 mg). After being stirred for 2 h at rt, the reaction mixture was diluted with $NaHCO_3$ solution (30 mL), and the solvent was removed by rotary evaporation. The residue was extracted with ethyl acetate (30 mL), washed with brine (30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (for **19a**, ethyl acetate/hexanes, 1/1; for **19b**, ethyl acetate/hexanes, 2/1) to give a colorless oil (**19a**, 0.50 g, 68%; **19b**, 0.26 g, 73%).

19a: ^1H NMR (200 MHz/$CDCl_3$) δ 7.51−7.30 (m, 5H), 5.74 and 4.70 (br d, 1H), 4.16−3.01 (m, 13H); EIMS *m*/*z* (relative intensity) 265 (M^+, 4), 234 (M^+ − OMe, 13), 105 ($PhCO^+$, 100).

19b: IR (neat) 3061, 1658 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$) δ 7.56−7.36 (m, 5H), 5.49 and 4.89 (br d, 1H), 4.75−4.49 (m, 4H), 4.40−3.82 (m, 3H), 3.58−3.05 (m, 10H); EIMS *m*/*z* (relative intensity) 325 (M^+, 3), 294 (M^+ − OMe, 2), 263 (M^+ − 2OMe, 1), 105 ($PhCO^+$, 100); HRMS ($C_{16}H_{23}NO_6$) calcd 325.1525, found 325.1524.

Preparation of Grignard Addition Products 21a, 21b, 22a and 22b, Method A. To a solution of the α-methoxybenzamide (**19a**: 0.11 g, 0.4 mmol; **19b**: 0.46 g, 1.4 mmol) in ether (for **19a**, 12 mL; for **19b**, 40 mL) was added *p*-(methoxybenzyl)magnesium chloride (1 M in THF) (for **19a**, 2.93 mL, 2.93 mmol; for **19b**, 7 mL, 7 mmol). After being refluxed for 15 h, the reaction was quenched with NH_4Cl and brine (1/1, 20 mL). The reaction mixture was extracted with ethyl acetate (50 mL × 3), dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (for **21a**, **22a** MeOH/ethyl acetate, 1/3; for **21b**, **22b**, MeOH/ethyl acetate, 1/5) to give a yellow oil (**21a**, 5 mg, 5%; **22a**, 91 mg, 87%) (**21b**, 6 mg, 1%; **22b**, 0.387 g, 89%).

21a: ^1H NMR (300 MHz/$CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.46−3.22 (m, 3H), 3.36 (s, 3H), 3.31 (s, 3H), 2.86−2.78 (m, 2H), 2.52 (br s, 1H); $[\alpha]_D$ = −39.1° (c = 0.64, $CDCl_3$), lit.[21] $[\alpha]_D$ = −63° (c = 0.979, $CDCl_3$).

21b: ^1H NMR (300 MHz/$CDCl_3$) δ 7.17 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.76 (d, J = 6.8 Hz, 1H), 4.71−4.60 (m, 3H), 4.21 (dd, J = 3.2, 2.0 Hz, 1H), 3.87 (d, J = 4.6, 1.3 Hz, 1H), 3.79 (s, 3H), 3.51−3.43 (m, 2H), 3.39 (s, 3H), 3.33 (s, 3H), 2.90−2.82 (m, 1H).

22a: IR (film) 3338 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.78 (s, 3H), 3.69 (dt, J = 4.8, 1.9 Hz, 1H), 3.38 (d, J = 3.9 Hz, 1H), 3.34 (s, 3H), 3.26 (s, 3H), 3.14−2.93 (m, 3H), 2.87 (dd, J = 13.6, 6.3 Hz, 1H), 2.75 (dd, J = 13.6, 6.3 Hz, 1H), 2.39 (br s, 1H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 157.9, 131.0, 129.7, 113.6, 89.6, 85.8, 65.4, 57.1, 56.4, 54.9, 50.2, 38.7; ^{13}C DEPT NMR (75 MHz/$CDCl_3$) δ 129.7 (CH), 113.6 (CH), 89.6 (CH_3), 85.8 (CH_3), 65.4 (CH_3), 57.1 (CH), 56.4 (CH), 54.9 (CH), 50.2 (CH_2), 38.7 (CH_2); $[\alpha]_D$ = +6.3° (c = 1.50, $CDCl_3$), lit.[21] $[\alpha]_D$ = +4° (c = 1.7, $CDCl_3$); HRMS ($C_{14}H_{21}NO_3$) calcd 251.1521, found 251.1525.

22b: IR (film) 3339 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$) δ 7.14 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.70−4.60 (m, 3H), 4.47 (d, J = 6.7 Hz, 1H), 4.06 (dt, J = 3.5, 1.4 Hz, 1H), 3.77 (dd, J = 4.6, 1.3 Hz, 1H), 3.75 (s, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 3.18−3.11 (m, 1H), 3.02 (d, J = 3.5Hz, 2H), 2.87 (dd, J = 13.6, 6.2 Hz, 1H), 2.77 (dd, J = 13.6, 8.0 Hz, 1H), 2.02 (br s, 1H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 158.0, 130. 9, 130.3, 129.9, 113.8, 95.6, 95.1, 85.6, 81.1, 66.1, 55.3, 55.1, 51.3, 38.7.

Method B. The procedure in method A was used except $MgBr_2$ etherate (1 equiv) was added before the addition of the Grignard reagent, and CH_2Cl_2 was used as solvent to give **21a**, 3.5%, **21b**, 3.3% / **22a**, 28%, **22b**, 39%.

Preparation of Diol 23. Pyrrolidine **22b** (0.15 g, 0.48 mmol) was refluxed in a mixture of MeOH/5 N HCl (1/1, 10 mL) for 22 h. The solution was then concentrated, made alkaline with Na_2CO_3, and extracted with $CHCl_3$ (2 × 20 mL). The aqueous phase was allowed to stand overnight at 5 °C, and the light yellow solid was collected by filtration. The crude product was purified by recrystallization from acetone/hexanes to give diol **23** as a white solid (48 mg, 45%): mp 125−128 °C (lit.[22] mp 130−131.5 °C).

Conversion of Amino Diol 23 to Ether Carbamate 24. To a solution of amino diol **23** (22 mg, 0.1 mmol) in aqueous Na_2CO_3 solution (44 M, 2 mL) and CH_2Cl_2 (2 mL) was added benzyl chloroformate (44 M in CH_2Cl_2, 2 mL) . After being stirred for 2 h, the reaction mixture was extracted with CH_2Cl_2 (30 mL × 3). The extract was dried over $MgSO_4$ and evaporated, and the residue was purified by preparative TLC (ethyl acetate/hexanes, 3/1) to give the carbamate diol as a colorless oil (13 mg, 40%): ^1H NMR (300 MHz/$CDCl_3$) δ 7.48−7.40 (m, 5H), 7.18 (br d, 1H), 7.04 (br d, 1H), 6.92 (br d, 2H), 5.15 (s, 2H), 4.14 (br s, 1H), 4.04−3.81 (m, 3H), 3.74 (s, 3H), 3.35 (dd, J = 7.1, 2.9 Hz, 1H), 3.15 (br d, 1H), 2.98 (dd, J = 9.2, 6.7 Hz, 1H), 2.24 (br d, 1H), 1.93 (br s, 1H).

To a solution of the above diol (13 mg, 0.036 mmol) in THF (5 mL) was added NaH (2 mg, 95%, 0.08 mmol) and MeI in THF (0.4 v/v%, 1 mL) at 0 °C. After being stirred for 1 h at 0 °C and then for 40 min at rt and refluxed for 2 h, the reaction mixture was diluted with NH_4Cl solution (10 mL) and extracted with ethyl acetate (20 mL × 3). The extract was dried over $MgSO_4$ and evaporated. The residue was purified by preparative TLC (ethyl acetate/hexanes, 1/3) to give dimethyl ether carbamate **24** as a colorless oil (12 mg, 87%): ^1H NMR (300 MHz/$CDCl_3$) δ 7.46−7.28 (m, 5H), 7.20 (d, J = 7.5 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.83 (dd, J = 10.0, 4.6 Hz, 2H),

5.25−5.09 (m, 2H), 3.98 and 3.67 (rotamers, m, 1H), 3.80 (br s, 5H), 3.54 (s, 2H), 3.41 (s, 3H), 3.28 and 3.08 (rotamers, m, 1H), 3.03 (d, J = 6.7 Hz, 3H), 2.73 (q, J = 12.1 Hz, 1H).

Hydrogenolysis of Benzyl Carbamate 24. A solution of benzyl carbamate **24** (12 mg, 0.031 mmol) in EtOH (3 mL) was hydrogenated for 0.5 h in the presence of 10% Pd/C (12 mg) at 1 atm of H_2. The catalyst was removed by filtration through a Celite pad and concentrated *in vacuo* to give the amine **22a** as a light yellow oil (6 mg, 77%): ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.16 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.71 (dt, J = 4.8, 1.9 Hz, 1H), 3.38 (d, J = 3.9 Hz, 1H), 3.35 (s, 3H), 3.28 (s, 3H), 3.14−2.93 (m, 3H), 2.86 (dd, J = 13.6, 6.3 Hz, 1H), 2.78 (dd, J = 13.6, 6.3 Hz, 1H), 2.39 (br s, 1H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 157.9, 131.2, 130.0, 113.9, 89.9, 86.1, 65.6, 57.3, 56.7, 55.2, 50.4, 38.9.

Synthesis of 2-(Trimethylsilyl)piperidine *o*-Aminobenzamide (39). To a solution of 2-(trimethylsilyl)piperidine (**38**,[24] 75 mg, 0.48 mmol) in 10.0 mL of CH_2Cl_2 and triethylamine (1.0 mL) was added *o*-nitrobenzoyl chloride (121 mg, 0.65 mmol) in 2.0 mL of CH_2Cl_2 at 0 °C. The reaction mixture was warmed to rt, stirred for 18 h and extracted with 5% HCl (10 mL × 2). The organic layer was washed with satd $NaHCO_3$ (10 mL × 2), dried with $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexanes, 1/1) to give 2-(trimethylsilyl)piperidine *o*-nitrobenzamide (yellow oil, 93 mg, 63%): ^{1}H NMR (200 MHz/$CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 6.8 Hz, 1H), 7.40−7.30 (m, 1H), 4.32, 3.96 (rotamers, 2br s, 1H), 3.27−3.05 (m, 2H), 1.89−1.47 (m, 6H), 0.14 (s, 9H); EIMS m/z (relative intensity) 306 (M^+, 2), 291 (M^+ − Me, 100), 150 (*o*-NO_2COPh^+, 39).

A solution of the above *o*-nitrobenzamide (63 mg, 0.21 mmol) in MeOH (10.0 mL) was hydrogenated for 1.5 h in the presence of 10% Pd/C (52 mg) at 1 atm of H_2. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexanes, 1/2) to give amide **39** as a yellow oil (56 mg, 97%): IR (film) 3458, 3346, 1614 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.17−7.02 (m, 2H), 6.73−6.66 (m, 2H), 4.20 (br s, 2H), 4.10 (br s, 1H), 3.59 (m, 1H), 3.13 (m, 1H), 1.78−1.41 (m, 6H), 0.97 (s, 9H); CIMS m/z (relative intensity) 277 (MH^+, 100), 261 (M^+ − Me, 30), 203 (M^+ − TMS, 2), 120 (*o*-NH_2PhCO^+, 20); HRMS ($C_{15}H_{24}N_2OSi$) calcd 276.1658, found 276.1647.

General Procedure for Allylation of α-Methoxybenzamides. To a solution of the α-methoxybenzamide (0.2−8 mmol) in CH_2Cl_2 (0.05 M) at −78 °C was added $TiCl_4$ (2 equiv, 1.0 M in CH_2Cl_2) followed by allyltrimethylsilane (2 equiv). The reaction mixture was allowed to warm to rt overnight, neutralized with saturated $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (25 mL × 3). The combined organic layer was washed with brine (50 mL × 2), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/hexanes, 1/1−2/1).

2-Allylpiperidine *o*-nitrobenzamide (72) (yellow oil, 79%) (20 h): ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.09−8.06 (m, 2H), 7.57−7.44 (m, 2H), 5.67, 5.39, 4.41, 3.64 (rotamers, br s, 1H), 4.95−4.92 (m, 3H), 3.25, 2.99, 2.79 (rotamers, br s, 2H), 2.50−2.40, 2.19 (rotamers, m, 2H), 1.54−1.34 (rotamers, br s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 167.6, 147.5, 138.1, 134.5, 116.6 (rotamers), 133.6, 117.7 (rotamers), 132.2, 129.2, 123.4, 121.4, 54.3, 36.9 (rotamers) 47.3, 42.9 (rotamers), 34.0, 28.1, 27.1, 25.5 (rotamers), 18.3; CIMS m/z (relative intensity) 275 (MH^+, 90), 233 (M^+ − C_3H_5, 100), 150 (*o*-NO_2PhCO^+, 20).

2-Allylpyrrolidine *o*-nitrobenzamide (73) (yellow oil, 85%) (2 d): ^{1}H NMR (200 MHz/$CDCl_3$) δ 8.35−8.20 (t, J = 14 Hz, 2H), 7.90−7.75 (d, J = 10 Hz, 1H), 7.65−7.50 (t, J = 8 Hz, 1H), 5.90−5.55 (m, 1H), 5.50−4.70 (m, 2H) 4.40−4.20 (br s, 1H), 3.95−3.10 (m, 2H), 2.70−2.55 (m, 1H), 2.45−2.20 (m, 1H), 2.10−1.60 (m, 4H); CIMS m/z (relative intensity) 261 (MH^+, 100), 219 (M^+ − C_3H_5, 50), 150 (*o*-NO_2PhCO^+, 20).

General Procedure for Hydrogenation of Allyl-Substituted *o*-Nitrobenzamides. The allyl benzamide (0.5−4.7 mmol) in dry methanol (0.05 M) was reduced in the presence of Pd/C (10%) under 1 atm of H_2 for 22 h. The solution was filtered through Celite, and the pad was rinsed with ethyl acetate (15 mL) followed by evaporation of the filtrate. Purification of the residue was done by flash column chromatography eluting with ethyl acetate/hexanes (1/1−3/1).

2-Propylpiperidine *o*-aminobenzamide (34) (yellow oil, 88%): ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.08 (t, J = 4.5 Hz, 1H), 6.60 (t, J = 7.6 Hz, 3H), 4.84, 4.51 (rotamers, br s, 1H), 3.75 (br s, 2H), 3.51, 2.96, 2.76 (rotamers, br s, 2H), 1.59 (br s, 6H), 1.41, 1.18, 1.11 (3br s, 7H); EIMS m/z (relative intensity) 246 (M^+, 16), 203 (M^+ − C_3H_7, 33), 120 (*o*-NH_2PhCO^+, 100).

2-Propylpyrrolidine *o*-aminobenzamide (50) (yellow oil, 92%): ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.18−7.10 (t, J = 7.9 Hz, 1H), 6.85−6.66 (m, 3H), 4.25 (br s, 1H), 3.75−3.50 (m, 2H), 3.40−3.34 (t, J = 5.6 Hz, 2H), 2.05−1.50 (m, 4H), 1.40−1.25 (m, 4H), 0.95−0.75 (m, 3H); EIMS m/z (relative intensity) 232 (M^+, 20), 189 (M^+ − C_3H_7, 19), 120 (*o*-NH_2PhCO^+, 100).

General Procedure for Zinc Reduction of Allyl *o*-Nitrobenzamides. The allyl *o*-nitrobenzamide (0.2−2.5 mmol) in ethyl acetate/Et_2O (1/1, 0.08 M) was treated with Zn dust (5 equiv) and glacial acetic acid. After 1 d at rt, the mixture was filtered through Celite, and the pad was washed with ethyl acetate (25 mL), followed by concentration of the filtrate. The residue was partitioned between ethyl acetate (3 × 25 mL) and H_2O (25 mL). The combined organics were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography, eluting with ethyl acetate/hexanes (2/1).

2-Allylpiperidine *o*-aminobenzamide (36) (yellow oil, 88%): IR (film) 3443, 3346, 1614 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.18−7.10 (t, J = 7.8 Hz, 1H), 6.79−6.61 (m, 3H), 5.76 (br s, 1H), 5.08−4.99 (m, 3H), 3.79 (br s, 2H), 2.92 (br s, 2H), 2.43−2.35 (m, 1H), 2.35−2.15 (m, 1H), 1.70−1.40 (br s, 6H); CIMS m/z (relative intensity) 245 (MH^+, 100) 203 (M^+ − C_3H_5, 40), 120 (*o*-NH_2PhCO^+, 20); HRMS ($C_{15}H_{20}N_2O$) calcd 244.1576, found 244.1573.

2-Allylpyrrolidine *o*-aminobenzamide (52) (yellow oil, 86%): IR (film) 3437, 3345, 1614 cm^{-1}; ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.20−7.10 (t, J = 6 Hz, 1 Hz), 6.85−6.65 (m, 3H), 5.95−5.70 (m, 1H), 5.15−4.85 (m, 2H), 4.32 (br s, 1H), 3.85−3.60 (br s, 2H), 3.45−3.30 (m, 2H), 2.75−2.55 (m, 1H), 2.45−2.20 (m, 1H), 2.00−1.60 (m, 4H); EIMS m/z (relative intensity) 230 (M^+, 13), 189 (M^+ − C_3H_5, 24), 120 (*o*-NH_2PhCO^+, 100); HRMS ($C_{14}H_{18}N_2O$) calcd 230.1419, found 230.1436.

General Oxidation Procedure Using $RuCl_2(PPh_3)_3$ as Catalyst. To a solution of the *o*-aminobenzamide (0.4−0.9 mmol) in MeOH (0.07 M) were added $NaNO_2$ (2 equiv) and $RuCl_2(PPh_3)_3$ (6 mol%). Methanolic HCl (3%, 3−4 equiv) was added over 5−10 min, and the reaction mixture was stirred at rt for the time indicated. The reaction mixture was diluted with saturated $NaHCO_3$ solution and concentrated *in vacuo*. The residue was extracted with ethyl acetate (20 mL × 3), washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative TLC (ethyl acetate/hexanes, 1/2−1/1).

Reaction of *o*-aminobenzamide 41 (1 h): **42** (19%), **43** (15%), **44** (42%).

Reaction of *o*-aminobenzamide 45 (1 h): **46** (33%), **47** (11%), **48** (3%), **49** (10%).

Reaction of *o*-aminobenzamide 28 (5 min): **30** (24%), **31** (23%), **32** (37%), **33** (7%).

Reaction of *o*-aminobenzamide 54 (1 h): **55** (46%), **56** (18%), **57** (10%), **58** (7%).

Acknowledgment. We are grateful to the National Institutes of Health (GM-32299) for support of this research.

Supporting Information Available: Copies of NMR spectra for new compounds (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961529A