Novel Methods for the Synthesis of Functionalized Indoles from Arylhydroxylamines and Activated Acetylenes

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Introduction

Many naturally occurring indoles possess important biological activity.[1-4] On the other hand, synthetic indoles with substituents at various positions have been used extensively in medicine and pharmacology,[1,5,6] as well as in holography.[1] Thus, the development of new, efficient methods[1-4,7-10] that lead to indoles is necessary. Herein, we report two novel methods for the synthesis of indoles which allow easy functionalization at almost all positions of the indole nucleus, particularly at the C-3 carbon.

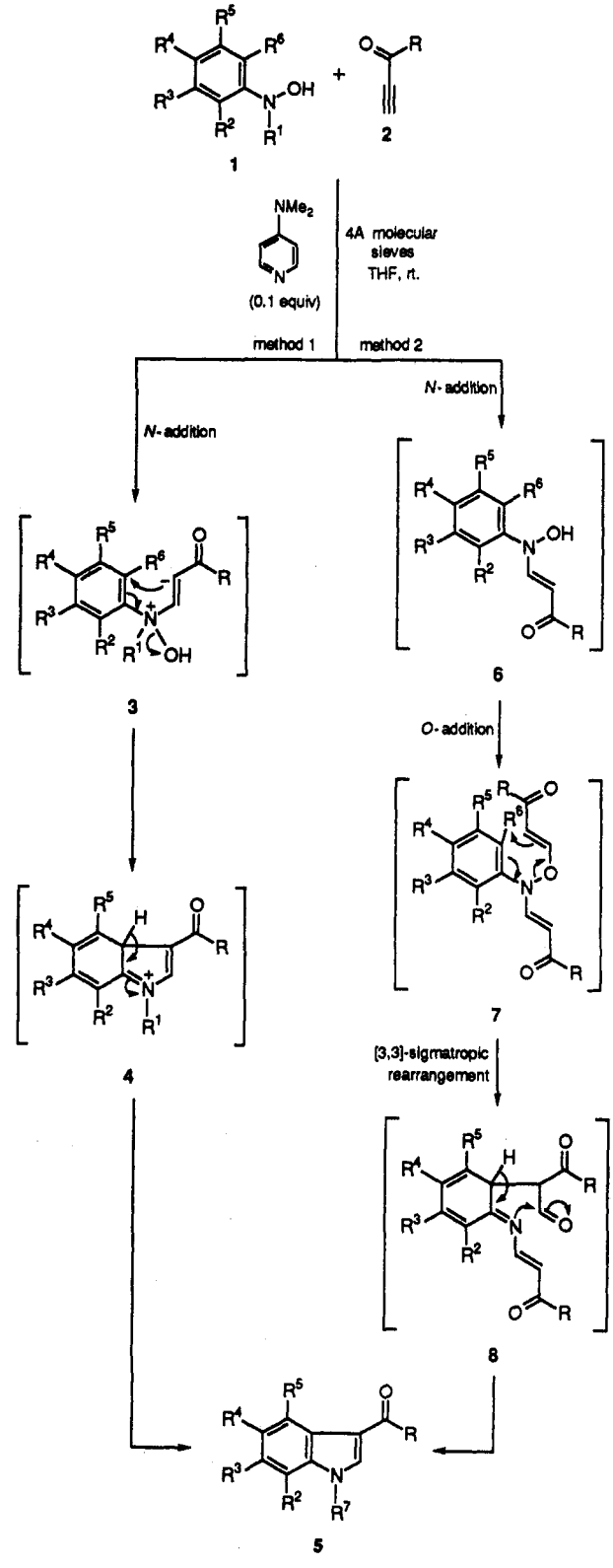
Results and Discussion

Our syntheses start with readily available arylhydroxylamines[11] and activated acetylenes. By deliberately controlling the nucleophilicity of the nitrogen and the oxygen atoms of the arylhydroxylamines, we have established two new methods for the construction of the indole nucleus under extremely mild conditions.

Method 1 is represented by the reaction of *N,N*-disubstituted arylhydroxylamines **1a–f**[12] with activated acetylenes **2** (R = H, Me, or OMe, 1.3–1.6 equiv) in the presence of 4-(dimethylamino)pyridine (DMAP, 0.1 equiv) and 4A molecular sieves in THF at room temperature for 3 days (Scheme 1). The desired indoles **5** were obtained in 52–82% yields (see Table 1). This method provides an easy entry to indoles bearing carbonyl functionalities, such as $-CO_2Me$, $-COMe$, and $-CHO$, at the crucial C-3 position.

The nitrogen atom of the *N,N*-disubstituted hydroxylamines **1a–f** seems to be more nucleophilic than the oxygen atom. Thus, the nitrogen atom preferentially added to the Michael acceptors **2** to give intermediates **3**, which underwent an intramolecular cyclization to form the pyrrole nucleus of indoles **5** via **4**. This postulation is

Scheme 1



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(12) Compounds **1a-e** were prepared from the corresponding nitrones by reduction with $NaBH_4$ in methanol at 10–15 °C in 10 min. Compound **1f** was prepared by condensation of *N*-phenylhydroxylamine with allyl bromide.

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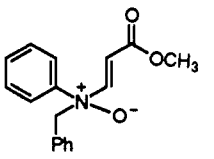
Table 1. Synthesis of Indoles (5) from Hydroxylamines (1) and Activated Acetylenes (2) with 0.1 Equiv of DMAP and 4A Molecular Sieves in THF at Room Temperature

	hydroxylamines 1						acetylenes 2		indoles 5[a]	
	R^1	R^2	R^3	R^4	R^5	R^6	R	equiv	R^7	yield (%)
a	CH_2Ph	H	H	H	H	H	OMe	1.3	CH_2Ph	82
b	CH_2Ph	Me	H	H	H	H	OMe	1.4	CH_2Ph	52
c	CH_2Ph	H	H	OPh	H	H	OMe	1.3	CH_2Ph	65
d	CH_2Ph	H	H	H	H	H	Me	1.5	CH_2Ph	71
e	CH_2Ph	H	H	Me	H	H	Me	1.6	CH_2Ph	61
f	$CH_2CH{=}CH_2$	H	H	H	H	H	H	1.3	$CH_2CH{=}CH_2$	77
g	H	H	H	H	H	H	Me	2.2	$CH{=}CHCOMe$	54
h	H	H	H	H	H	H	OMe	2.1	$CH{=}CHCO_2Me$	72
i	H	H	H	Me	H	H	OMe	3.0	$CH{=}CHCO_2Me$	66
j	H	H	H	Et	H	H	OMe	4.5	$CH{=}CHCO_2Me$	64
k	H	Ph	H	H	H	H	OMe	4.0	$CH{=}CHCO_2Me$	62
l	H	H	H	OPh	H	H	OMe	4.0	$CH{=}CHCO_2Me$	63
m	H	H	H	F	H	H	OMe	4.0	$CH{=}CHCO_2Me$	63
n	H	H	CF_3	H	H	H	OMe	4.0	$CH{=}CHCO_2Me$	52[b]
o	H	H	H	H	NMe_2	H	OMe	4.0	$CH{=}CHCO_2Me$	61[b]
p	H	CF_3	H	H	H	H	OMe	2.4	H	78
q	H	H	H	H	H	OMe	OMe	4.0	$CH{=}CHCO_2Me$	62
r	H	H	OEt	H	H	OEt	OMe	4.2	$CH{=}CHCO_2Me$	45

[a] R^2–R^5 in indoles 5 are the same as those in hydroxylamines 1. [b] The overall yields of the C-4 and the C-6 isomers.

made on the basis of Winterfeldt and Krohn's report on similar additions.[13]

To obtain evidence to support the formation of the intermediate zwitterionic species 3 in the process, we carried out a control experiment by treating hydroxylamine 1a with methyl propiolate 2 (R = OCH_3) in methanol. Enamine *N*-oxide intermediate 9 was isolated, which came directly from 3 by proton exchange between the hydroxyl group and the vinylic carbanion moiety. The ^1H NMR



9

spectrum of 9 exhibited a singlet at 3.76 ppm for the three OCH_3 protons, a singlet at 4.91 ppm for the two $-CH_2Ph$ protons, two doublets with a coupling constant of 12.5 Hz at 5.43 and 7.95 ppm for the $COCH{=}CHN^+$ protons, and a multiplet between 7.11–7.45 for phenyl protons. Relative to those in $PhN(OR)CH_2Ph$ (R = H, COMe, SO_2PhMe), the characteristic proton signals of the $-CH_2Ph$ in the enamine *N*-oxide 9 were shifted downfield by 0.40–0.50 ppm. This is ascribed to the deshielding effect resulting from the electron-deficient ammonium center in 9.

Furthermore, an intense peak appeared at *m/e* 267 ($M^{\bullet+}$–16, 32) in the mass spectrum of 9. This also indicated that species 9 contained an enamine *N*-oxide moiety, which often loses an oxygen atom under mass spectroscopic conditions.[14,15] The appearance of other characteristic fragments in the mass spectrum provided additional support of our structural assignment for the species 9, including *m/e* 252 ($M^{\bullet+}$–O–$^{\bullet}CH_3$), 236 ($M^{\bullet+}$–O–$^{\bullet}OCH_3$), and 208 ($M^{\bullet+}$–O–$^{\bullet}CH_3$–CO_2).

Our second new synthetic method is exemplified by the reaction of *N*-monosubstituted hydroxylamines 1g–r with activated acetylenes 2 (R = OMe, >2.0 equiv) in the presence of DMAP (0.1 equiv) and 4A molecular sieves in THF at room temperature for 2 days (Scheme 1). Indoles with various substituents on the benzene nucleus were isolated in good yields (5g–r in Table 1). The $-CH{=}CHCO_2Me$ group at the *N*-1 position could either be removed by hydrolysis or be modified further for the synthesis of more complex indole derivatives.

The "one-flask" process (i.e., method 2 in Scheme 1) involved two consecutive Michael additions, followed by a [3,3]-sigmatropic rearrangement. In the first Michael addition, the nucleophilic nitrogen center of 1 added to the first equivalent of acetylenes 2 to give tertiary hydroxylamine intermediates 6. The nitrogen atom in 6 is less nucleophilic than the oxygen atom because the unshared electron pair of the nitrogen can be delocalized over the electron-withdrawing moiety $-CH{=}CHCO_2Me$. This contrasted with the nucleophilicity of nitrogen and oxygen in $PhN(OH)CH_2Ph$ and $PhN(OH)CH_2CH{=}CH_2$, used in method 1. Consequently, the oxygen atom of 6 added to the second equivalent of acetylenes 2 to give intermediates 7, which underwent a [3,3]-sigmatropic rearrangement to afford indoles 5, via 8. This method, which allows the synthesis of indoles directly from *N*-monosubstituted arylhydroxylamines, differs from the procedure developed by Toyota and Fukumoto,[16] who reacted *N*-phenylbenzohydroxamic acid with methyl propiolate to give methyl 1-(benzyloxycarbonyl)indole-3-carboxylate.

Padwa and Wong[17] reported that, in the absence of a base, reaction between hydroxylamines with acetylenes leads to isoxazolidines via a nitrone intermediate. In contrast, we were able to obtain an entirely different class of compounds—indoles—by using the same types of starting materials in the presence of a catalytic amount of DMAP. This strong organic base has been used as a highly active catalyst in numerous organic reactions.[18,19] We believe that DMAP can efficiently remove a proton α to the carbonyl group of nitrones 10 to give *N*-oxide 11 (Scheme 2). This oxide reacts with the second equivalent of acetylenes 2 in situ through *O*-addition and then produces the desired indoles 5 as shown in Scheme 1. Use of other organic bases, including triethylamine, ethyldi-

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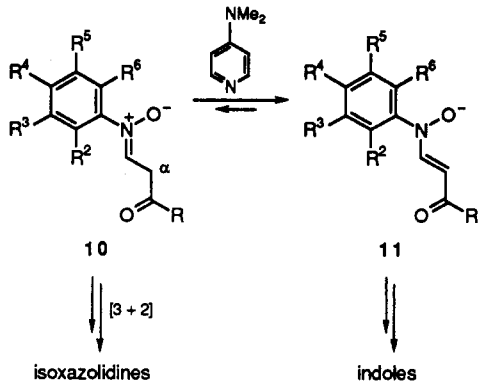
Scheme 2



isopropylamine, and 1,4-diazabicyclo[2.2.2]octane, did not produce the desired indoles in significant amounts. In addition, we found that the indolization can be performed in various solvents, such as dichloromethane, ether, and THF, among which THF provided the most satisfactory results.

The electron-withdrawing group $-CF_3$, attached to the C-2 position of the phenyl ring, significantly decreased the nucleophilicity of the nitrogen in an *N*-monosubstituted arylhydroxylamine (e.g., **1p**). Thus, upon treatment with an excess of methyl propiolate, [2-(trifluoromethyl)-phenyl]hydroxylamine (**1p**) reacted with only 1 equiv of the Michael acceptor at its oxygen center. Consequently, we obtained indole **5p** (78% yield), which did not bear the $-CH{=}CHCO_2Me$ substituent at the N-1 position. From arylhydroxylamines with an alkoxyl group at the C-2 position (e.g., **1q** and **1r**), we obtained indole products through an "*ipso*" substitution. Although the mechanism for the dealkoxylation process is not clear at this stage, these reactions provide a highly regioselective route to indoles with a substituent on the benzene ring. This was evidenced by the exclusive formation of **5q** from **1q** and **5r** from **1r**.

Conclusion

Two novel methods have been developed for the synthesis of indoles from arylhydroxylamines and activated acetylenes. These methods can lead to indole products bearing various attachments at the N-1, C-3, and all positions on the benzene nucleus; the attachments include $-CH_2Ph$, $-CH_2CH{=}CH_2$, $-CO_2Me$, -COMe, -CHO, Me, Et, Ph, -OMe, -OEt, -OPh, -F, $-CF_3$, and $-NMe_2$. The extremely mild reaction conditions, regioselectivity, and simple procedure are all valuable features of these new synthetic methods.

Experimental Section

General Procedure. All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen, unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Mixtures of ethyl acetates and hexanes were used as eluants. Gas chromatographic analyses were performed on a Hewlett-Packard 5890 Series II instrument equipped with a 25-m cross-linked methyl silicone gum capillary column (0.32-mm i.d.). The conditions for measurement of the retention time (t_R) are as follows: the temperature was 260 °C for the injection port, and temperature program was set at 250 °C isothermally. Purification by gravity column chromatography was carried out by use of Merck Reagents silica gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Elemental analyses were carried out on a Heraeus CHN-O-RAPID element analyzer at the National Cheng-Kung University.

Standard Procedure for the Synthesis of Substituted 1*H*-Indoles. To a THF solution of *N*-arylhydroxylamine (1.0 equiv) and 4A molecular sieves was added DMAP (0.1 equiv) at 0 °C. After 10 min, an activated acetylene (1.3–4.5 equiv) was added into the solution, which was stirred at 0 °C for an additional 1 h and room temperature for 48–70 h. Then EtOAc (5.0 mL) was added to the cloudy brown solution. After filtration, the organic solution was washed with water (3 × 20 mL) and brine, dried over $MgSO_4$(s), and condensed under reduced pressure. The resultant oil was purified by use of a chromatotron with EtOAc/hexanes = 3/7 as eluant.

1-Benzyl-1*H*-indole-3-carboxylic Acid Methyl Ester (5a). The standard procedure was followed by use of *N*-benzyl-*N*-phenylhydroxylamine (86.2 mg, 0.426 mmol, 1.0 equiv), THF (15.0 mL), 4A molecular sieves (0.80 g), DMAP (6.0 mg, 0.049 mmol), and methyl propiolate (54.0 mg, 0.562 mmol, 1.24 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5a** as a white solid in 82% yield (95.6 mg, 0.361 mmol): mp 67.0–67.5 °C; TLC R_f 0.15 (10% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 7.51 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.91 (s, 3 H, OCH_3), 5.33 (s, 2 H, CH_2Ph), 7.16 (d, 1 H, J = 7.8 Hz, Ar: 7-H), 7.24–7.33 (m, 7 H, Ph + Ar: 5-H, 6-H), 7.85 (s, 1 H, Ar: 2-H), 8.20 (d, 1 H, J = 7.2 Hz, Ar: 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.48 (t), 50.81 (q), 107.56 (s), 110.38 (d), 121.86 (d), 122.14 (d), 123.06 (d), 126.92 (s), 127.18 (d), 128.24 (d), 129.09 (d), 134.72 (d), 136.06 (s), 136.91 (s), 165.72 (s); IR (KBr) 3118 (m, ArH), 3034 (m), 2948 (m), 1706 (s, C=O), 1540 (s), 1473 (m, CH), 1448 (m, CH), 1404 (m), 1274 (m), 1252 (s), 1186 (s), 1151 (s), 1099 (s), 947 (m) cm^{-1}; MS *m/e* (relative intensity) 265 (M^+, 67), 234 (19), 204 (3.3), 146 (2.1), 115 (2.3), 91 (100), 65 (9.2); exact mass calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1100. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70; N, 5.28. Found: C, 76.93; H, 5.68; N, 5.39.

1-Benzyl-7-methyl-1*H*-indole-3-carboxylic Acid Methyl Ester (5b). The standard procedure was followed by use of *N*-benzyl-*N*-(2-methylphenyl)hydroxylamine (53.4 mg, 0.251 mmol, 1.0 equiv), THF (5.0 mL), 4A molecular sieves (0.40 g), DMAP (4.0 mg, 0.033 mmol), and methyl propiolate (27.0 mg, 0.361 mmol, 1.4 equiv). After 70 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5b** as a white solid in 52% yield (36.4 mg, 0.131 mmol): mp 104–105 °C; TLC R_f 0.30 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 8.41 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.54 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 5.62 (s, 2 H, CH_2Ph), 6.95–6.98 (m, 2 H, Ar: 5-H, 6-H), 7.15–7.32 (m, 5 H, Ph), 7.81 (s, 1 H, Ar: 2-H), 8.13 (d, 1 H, J = 8.2 Hz, Ar: 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.41 (q), 50.95 (q), 52.93 (t), 119.74 (s), 121.68 (s), 124.99 (d), 125.39 (s), 125.56 (d), 127.81 (s), 128.96 (d), 128.99 (d), 129.09 (d), 136.48 (d), 136.50 (s), 137.95 (d), 136.51 (d), 164.58 (s). IR (KBr) 3122 (m, ArH), 2952 (m), 1705 (s, C=O), 1606 (m), 1545 (s), 1499 (m, CH), 1457 (m, CH), 1417 (m), 1389 (s), 1361 (m), 1202 (s), 1013 (s), 977 (s), 889 (m) cm^{-1}; MS *m/e* (relative intensity) 279 (M^+, 62.1), 248 (7.3), 220 (3.2), 129 (2.1), 91 (100), 65 (6.8); exact mass calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1262. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.38; H, 6.14; N, 5.02. Found: C, 77.34; H, 6.10; N, 5.12.

1-Benzyl-5-phenoxy-1*H*-indole-3-carboxylic Acid Methyl Ester (5c). The standard procedure was followed by use of *N*-benzyl-*N*-(4-phenoxyphenyl)hydroxylamine (167.0 mg, 0.571 mmol, 1.0 equiv), THF (16.0 mL), 4A molecular sieves (0.80 g), DMAP (7.0 mg, 0.057 mmol), and methyl propiolate (62.0 mg, 0.737 mmol, 1.3 equiv). After 70 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5c** as a white solid in 65% yield (134.0 mg, 0.373 mmol): mp 108–109 °C; TLC R_f 0.26 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 19.35 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3 H, OCH_3), 5.36 (s, 2 H, CH_2Ph), 7.00–7.37 (m, 12 H, Ph + Ar: 6-H, 7-H), 7.88 (s, 1 H, Ar: 2-H), 7.90 (s, 1 H, Ar: 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.78 (q), 50.78 (t), 107.55 (s), 111.42 (d), 112.32 (d), 116.54 (d), 117.77 (d), 122.45 (s), 127.24 (d), 127.86 (s), 128.37 (d), 129.17 (d), 129.72 (d), 133.71 (s), 135.55 (d), 135.87 (s), 152.34 (s), 159.06 (s), 165.51 (s); IR (KBr) 3072 (m, ArH), 3037 (w), 2947 (m), 1699 (s, C=O), 1598 (s), 1578 (s), 1531 (s), 1494 (s), 1477 (s), 1455 (s, CH), 1432 (s, CH), 1373 (s), 1247 (s),

1225 (s), 1200 (s), 1143 (s), 1076 (s), 899 (s), 889 (s) cm^{-1}; MS *m/e* (relative intensity) 357 (M$^+$, 100), 326 (8.6), 298 (4.2), 206 (3.2), 91 (89.5), 65 (6.3); exact mass calcd for $C_{23}H_{19}NO_3$ 357.1365, found 357.1363. Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.28; H, 5.36; N, 3.92. Found: C, 77.24; H, 5.33; N, 3.95.

3-Acetyl-1-benzyl-1*H*-indole (5d). The standard procedure was followed by use of *N*-benzyl-*N*-phenylhydroxylamine (97.7 mg, 0.491 mmol, 1.0 equiv), THF (7.0 mL), 4A molecular sieves (0.50 g), DMAP (6.5 mg, 0.053 mmol), and 3-butyn-2-one (50.9 mg, 0.748 mmol, 1.5 equiv). After 28 h, the reaction was worked up and the residue was purified by use of a chromatotron to give **5d** as a white solid in 71% yield (86.7 mg, 0.347 mmol): mp 104–105 °C; TLC R_f 0.12 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 6.79 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, 3 H, CH_3), 5.35 (s, 2 H, CH_2Ph), 7.16–7.19 (m, 2 H, Ar: 6-H, 7-H), 7.28–7.36 (m, 6 H, Ph + Ar: 5-H), 7.77 (s, 1 H, Ar: 2-H), 8.42 (d, 1 H, J = 7.1 Hz, Ar: 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.05 (q), 49.97 (t), 109.92 (s), 116.67 (d), 122.03 (s), 122.93 (d), 125.97 (d), 126.43 (d), 126.45 (s), 128.43 (s), 128.47 (d), 135.12 (d), 135.48 (d), 136.50 (d), 192.58 (s); IR (KBr) 3113 (m, ArH), 3036 (w), 2929 (w), 1704 (s, C=O), 1577 (s), 1502 (s), 1444 (w), 1364 (w), 1343 (s), 1245 (w), 1192 (s), 1154 (s), 1092 (w), 972 (w), 841 (w) cm^{-1}; MS *m/e* (relative intensity) 249 (M$^+$, 71.6), 234 (65.3), 206 (3.2), 130 (2.6), 115 (2.8), 91 (100), 65 (13.7); exact mass calcd for $C_{17}H_{15}NO$ 249.1154, found 249.1154. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.89; H, 6.07; N, 5.62. Found: C, 81.85; H, 6.05; N, 5.52.

3-Acetyl-1-benzyl-5-methyl-1*H*-indole (5e). The standard procedure was followed by use of *N*-benzyl-*N*-(4-methylphenyl)-hydroxylamine (103 mg, 0.484 mmol, 1.0 equiv), THF (6.0 mL), 4A molecular sieves (0.50 g), DMAP (7.0 mg, 0.057 mmol), and 3-butyn-2-one (55.2 mg, 0.813 mmol, 1.6 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5e** as a white solid in 61% yield (77.6 mg, 0.295 mmol): mp 140.5–142.0 °C; TLC R_f 0.31 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 8.39 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.48 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 5.31 (s, 2 H, CH_2Ph), 7.08–7.40 (m, 7 H, Ph + Ar: 6-H, 7-H), 7.72 (s, 1 H, Ar: 2-H), 8.23 (s, 1 H, Ar: 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.21 (q), 27.31 (q), 50.50 (t), 109.91 (d), 117.09 (s), 122.43 (d), 125.11 (d), 126.79 (s), 127.04 (d), 128.25 (d), 129.12 (d), 129.29 (s), 132.44 (s), 135.33 (d), 136.11 (s), 193.46 (s); IR (KBr) 3110 (m, ArH), 2921 (w), 1638 (s, C=O), 1534 (s), 1399 (s), 1247 (w), 1200 (s), 1188 (s), 1096 (w), 940 (w) cm^{-1}; MS *m/e* (relative intensity) 263 (M$^+$; 75.8), 248 (78.9), 220 (5.8), 144 (3.2), 115 (2.6), 91 (100), 65 (11.6); exact mass calcd for $C_{18}H_{17}NO$ 263.1310, found 263.1288. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.09; H, 6.51; N, 5.32. Found: C, 82.14; H, 6.49; N, 5.38.

1-Allyl-1*H*-indole-3-carboxaldehyde (5f). The standard procedure was followed by use of *N*-allyl-*N*-phenylhydroxylamine (250.0 mg, 1.678 mmol, 1.0 equiv), THF (8.0 mL), 4A molecular sieves (2.48 g), DMAP (20.5 mg, 0.168 mmol), and propargyl aldehyde (117.8 mg, 2.18 mmol, 1.3 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5f** as a white solid in 77% yield (239.0 mg, 1.292 mmol): mp 72–73 °C; TLC R_f 0.12 (20% EtOAc in hexanes as eluant); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (d, 2 H, J = 5.6 Hz, NCH_2), 5.26 (dd, 2 H, J = 10.3, 17.1 Hz, C=CH_2), 5.99–6.06 (m, 1 H, HC=), 7.20–7.40 (m, 3 H, Ar: 5-H, 6-H, 7-H), 7.73 (s, 1 H, Ar: 2-H), 8.30–8.33 (m, 1 H, Ar: 4-H), 10.01 (s, 1 H, CHO). IR (KBr) 3001 (m), 2802 (w), 1655 (s, C=O), 1608 (m), 1531 (s), 1466 (s, CH), 1402 (s, CH), 1208 (s), 1167 (s), 1132 (w), 1032 (w), 926 (w), 756 (s) cm^{-1}; MS *m/e* (relative intensity) 185 (M$^+$, 100), 184 (68.9), 158 (8.5), 156 (38.7), 130 (8.9), 116 (11.9), 89 (11.8), 63 (7.3); exact mass calcd for $C_{12}H_{11}NO$ 185.0841, found 185.0700. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.57. Found: C, 77.78; H, 5.95; N, 7.61.

3-Acetyl-1-(2-oxo-3-buten-4-yl)-1*H*-indole (5g). The standard procedure was followed by use of *N*-phenylhydroxylamine (215.0 mg, 1.95 mmol, 1.0 equiv), THF (8.0 mL), 4A molecular sieves (1.5 g), DMAP (22.8 mg, 0.186 mmol), and 3-butyn-2-one (281.0 mg, 4.41 mmol, 2.2 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5g** as a white solid in 54% yield (241.0 mg, 1.06 mmol): mp 191–192 °C; TLC R_f 0.13 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 7.60 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.410 (s, 3 H, CH_3), 2.601 (s, 3 H, CH_3), 6.549 (d, 1 H, J = 14 Hz, NC=CH), 7.321–7.462 (m, 2 H, Ar: 5-H, 6-H), 7.615 (d, 1 H, J = 7.1 Hz, Ar: 7-H), 8.028 (s, 1 H, Ar: 2-H), 8.183 (d, 1 H, J = 14 Hz, NCH=), 8.394 (d, 1 H, J = 7.1 Hz, Ar: 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.81 (q), 29.05 (q), 110.02 (d), 112.49 (d), 121.71 (s), 123.17 (d), 124.48 (d), 125.18 (d), 126.94 (s), 129.29 (d), 135.19 (d), 136.69 (s), 191.43 (s), 196.03 (s); IR (KBr) 3110 (m), 3076 (m, Ar-H), 1700 (s, C=O), 1653 (s, C=O), 1559 (s, C=C), 1464 (s, C-H), 1389 (s), 1267 (s), 1231 (s), 1160 (s), 975 (s), 852 (s), 740 (s) cm^{-1}; MS *m/e* (relative intensity) 227 (M$^+$, 51.9), 212 (100), 170 (17.1), 143 (5.1), 115 (4.1), 98 (3.3), 44 (7.1); exact mass calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0950. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.98; H, 5.77; N, 6.16. Found: C, 73.49; H, 5.48; N, 5.89.

1-[2-(Methoxycarbonyl)vinyl]-1*H*-indole-3-carboxylic Acid Methyl Ester (5h). The standard procedure was followed by use of *N*-phenylhydroxylamine (272.0 mg, 2.50 mmol, 1.0 equiv), THF (12.0 mL), 4A molecular sieves (1.57 g), DMAP (22.8 mg, 0.186 mmol), and methyl propiolate (462.0 mg, 5.45 mmol, 2.1 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5h** as a white solid in 72% yield (465.0 mg, 1.80 mmol): mp 149–150 °C; TLC R_f 0.28 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 5.60 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.15 (d, 1 H, J = 14.0 Hz, NC=CH), 7.31–7.44 (m, 2 H, Ar: 5-H, 6-H), 7.62 (d, 1 H, J = 8.1 Hz, Ar: 7-H), 8.10 (s, 1 H, Ar: 2-H), 8.19 (d, 1 H, J = 8.1 Hz, Ar: 4-H), 8.26 (d, 1 H, J = 14 Hz, NCH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.36 (q), 51.71 (q), 103.84 (d), 110.09 (d), 113.11 (s), 122.12 (d), 123.76 (d), 124.64 (d), 126.94 (s), 129.17 (d), 136.26 (s), 136.32 (d), 164.24 (s), 166.83 (s); IR (KBr) 3118 (m), 3076 (m, ArH), 2947 (m), 1707 (s, C=O), 1639 (s, C=O), 1549 (s, C=C), 1467 (s, CH), 1438 (s, CH), 1377 (s), 1303 (s), 1261 (s), 1226 (s), 1167 (s), 976 (s), 852 (s), 776 (s), 744 (s) cm^{-1}; MS *m/e* (relative intensity) 259 (M$^+$, 100), 228 (89.1), 196 (6.2), 185 (16.1), 169 (10.2), 140 (9.1), 114 (6.9), 98 (13.1), 44 (14.1); exact mass calcd for $C_{14}H_{13}NO_4$ 259.0844, found 259.0848. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.49; H, 4.68; N, 5.24.

1-[2-(Methoxycarbonyl)vinyl]-5-methyl-1*H*-indole-3-carboxylic Acid Methyl Ester (5i). The standard procedure was followed by use of *N*-(4-methylphenyl)hydroxylamine (60.6 mg, 0.493 mmol, 1.0 equiv), THF (8.0 mL), 4A molecular sieves (0.60 g), DMAP (6.5 mg, 0.053 mmol), and methyl propiolate (122.9 mg, 1.46 mmol, 3.0 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5i** as a white solid in 66% yield (89.4 mg, 0.327 mmol): mp 140.5–142.0 °C; TLC R_f 0.31 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 6.99 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.50 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.11 (d, 1 H, J = 14.2 Hz, NC=CH), 7.21 (d, 1 H, J = 8.4 Hz, Ar: 7-H), 7.46 (d, 1 H, J = 8.4 Hz, Ar: 6-H), 7.97 (s, 1 H, Ar: 4-H), 8.02 (s, 1 H, Ar: 2-H), 8.18 (d, 1 H, J = 14.2 Hz, NCH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.22 (q), 51.21 (q), 51.58 (q), 103.19 (d), 109.64 (d), 112.52 (s), 121.69 (d), 125.89 (d), 126.98 (s), 129.15 (d), 133.38 (s), 134.39 (s), 136.38 (d), 164.23 (s), 166.85 (s); IR (KBr) 3120 (m, ArH), 3074 (w), 3001 (w), 2950 (m), 1710 (s, C=O), 1641 (s, C=O), 1548 (s, C=C), 1433 (s, CH), 1407 (s, CH), 1372 (s), 1259 (s), 1170 (s), 955 (s), 845 (m), 768 (s) cm^{-1}; MS *m/e* (relative intensity) 273 (M$^+$, 30.1), 252 (25.2), 242 (24.4), 221 (100), 193 (21.9), 147 (13.8), 121 (15.1), 106 (15.1), 85 (17.1); exact mass calcd for $C_{15}H_{15}NO_4$ 273.1001, found 273.1006. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.82; H, 5.51; N, 5.12.

5-Ethyl-1-[2-(methoxycarbonyl)vinyl]-1*H*-indole-3-carboxylic Acid Methyl Ester (5j). The standard procedure was followed by use of *N*-(4-ethylphenyl)hydroxylamine (58.8 mg, 0.429 mmol, 1.0 equiv), THF (6.0 mL), 4A molecular sieves (0.67 g), DMAP (7.3 mg, 0.060 mmol), and methyl propiolate (160.7 mg, 1.91 mmol, 4.5 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5j** as a white solid in 64% yield (79.0 mg, 0.275 mmol): mp 131.0–132.5 °C; TLC R_f 0.29 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 8.15 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 3 H, J = 7.6 Hz, CH_3), 2.77 (q, 2 H, J = 7.6 Hz, CH_2), 3.82 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.10 (d, 1 H, J = 14.2 Hz, NC=CH), 7.23 (d, 1 H, J = 8.4 Hz, Ar: 7-H), 7.48 (d, 1 H, J =

8.4 Hz, Ar: 6-H), 7.98 (s, 1 H, Ar: 4-H), 8.02 (s, 1 H, Ar: 2-H), 8.18 (d, 1 H, J = 14.2 Hz, NCH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.16 (q), 28.93 (t), 51.41 (q), 51.77 (q), 103.58 (d), 110.03 (d), 113.00 (s), 120.83 (d), 125.17 (d), 127.32 (s), 129.34 (d), 134.84 (s), 136.71 (d), 140.32 (s), 164.40 (s), 167.02 (s); IR (KBr) 3119 (w), 3073 (w), 2949 (m), 2918 (m), 2849 (m), 1706 (s, C=O), 1632 (s, C=O), 1551 (s, C=C), 1473 (s, CH), 1434 (s, CH), 1372 (s), 1248 (s), 1161 (s), 953 (s), 887 (m), 841 (s), 796 (s), 744 (s) cm^{-1}; MS m/e (relative intensity) 287 (M^+, 100), 272 (98), 256 (39.4), 228 (6.4), 156 (7.4), 66 (15.3); exact mass calcd for $C_{16}H_{17}NO_4$ 287.1157, found 287.1136. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.53; H, 5.95; N, 4.83.

1-[2-(Methoxycarbonyl)vinyl]-7-phenyl-1*H*-indole-3-carboxylic Acid Methyl Ester (5k). The standard procedure was followed by use of *N*-(2-phenylphenyl)hydroxylamine (63.5 mg, 0.343 mmol, 1.0 equiv), THF (6.0 mL), 4A molecular sieves (0.64 g), DMAP (6.2 mg, 0.051 mmol), and methyl propiolate (115.4 mg, 1.37 mmol, 4.0 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5k** as a white solid in 62% yield (89.4 mg, 0.327 mmol): mp 127.5–129.0 °C; TLC R_f 0.28 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 15.83 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 5.86 (d, 1 H, J = 14.0 Hz, NC=CH), 7.23–7.55 (m, 7 H, Ph + Ar: 5-H, 6-H), 7.66 (d, 1 H, J = 14.0 Hz, NCH=), 8.10 (s, 1 H, Ar: 2-H), 8.26 (d, 1 H, J = 7.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.43 (q), 51.54 (q), 103.82 (d), 112.99 (s), 121.44 (d), 123.41 (d), 127.59 (d), 127.97 (s), 128.00 (s), 128.22 (d), 128.98 (d), 129.43 (d), 130.11 (d), 133.95 (s), 138.54 (s), 139.52 (d), 164.57 (s), 166.51 (s); IR (KBr) 3124 (m), 3093 (w, ArH), 2991 (w), 2946 (m), 1705 (s, C=O), 1637 (s, C=O), 1557 (s, C=C), 1421 (s, CH), 1249 (s), 1117 (s), 1054 (m), 961 (m), 801 (m), 760 (m), 747 (m), 705 (m) cm^{-1}; MS m/e (relative intensity) 335 (M^+, 100), 304 (38.1), 275 (15.6), 262 (14.6), 244 (38.8), 217 (24.1), 190 (8.2), 163 (3.4), 122 (5.1), 107 (4.8); exact mass calcd for $C_{20}H_{17}NO_4$ 335.1157, found 335.1154. Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.48; H, 5.11; N, 4.21.

1-[2-(Methoxycarbonyl)vinyl]-5-phenoxy-1*H*-indole-3-carboxylic Acid Methyl Ester (5l). The standard procedure was followed by use of *N*-(4-phenoxyphenyl)hydroxylamine (71.7 mg, 0.357 mmol, 1.0 equiv), THF (8.0 mL), 4A molecular sieves (0.73 g), DMAP (5.6 mg, 0.046 mmol), and methyl propiolate (122.9 mg, 1.46 mmol, 4.0 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5l** as a light orange solid in 63% yield (79.3 mg, 0.226 mmol): mp 211–212 °C; TLC R_f 0.25 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 27.77 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.19 (d, 1 H, J = 14.1 Hz, NC=CH), 7.03 (d, 1 H, J = 8.3 Hz, Ar: 7-H), 7.10–7.40 (m, 5 H, Ph), 7.61 (d, 1 H, J = 8.3 Hz, Ar: 6-H), 7.87 (d, 1 H, J = 2.3 Hz, Ar: 4-H), 8.14 (s, 1 H, Ar: 2-H), 8.24 (d, 1 H, J = 14.1 Hz, NCH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.53 (q), 51.89 (q), 104.26 (d), 111.34 (d), 112.52 (d), 113.16 (s), 117.74 (d), 118.06 (d), 122.88 (d), 128.23 (s), 129.72 (d), 130.19 (d), 132.88 (s), 136.57 (d), 153.71 (s), 158.18 (s), 164.21 (s), 166.89 (s); IR (KBr) 3122 (m), 3084 (w, ArH), 2944 (w), 1721 (s, C=O), 1647 (s, C=O), 1549 (s, C=C), 1469 (s), 1433 (s, CH), 1369 (m), 1214 (s), 1041 (s), 957 (s), 905 (m), 756 (s) cm^{-1}; MS m/e (relative intensity) 351 (M^+, 100), 320 (52.5), 277 (5.4), 160 (6.4); exact mass calcd for $C_{20}H_{17}NO_5$ 351.1107, found 351.1089. Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 67.57; H, 4.93; N, 3.93.

5-Fluoro-1-[2-(methoxycarbonyl)vinyl]-1*H*-indole-3-carboxylic Acid Methyl Ester (5m). The standard procedure was followed by use of *N*-(4-fluorophenyl)hydroxylamine (35.6 mg, 0.280 mmol, 1.0 equiv), THF (6.0 mL), 4A molecular sieves (0.60 g), DMAP (3.3 mg, 0.027 mmol), and methyl propiolate (94.5 mg, 1.12 mmol, 4.0 equiv). After 48 h, the reaction was worked up and the residue was purified by use of a chromatotron to give **5m** as a white solid in 63% yield (48.8 mg, 0.176 mmol): mp 155–156 °C; TLC R_f 0.33 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 5.43 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 6.17 (d, 1 H, J = 14.2 Hz, NC=CH), 7.16 (dt, 1 H, J = 2.6, 8.9 Hz, Ar: 7-H), 7.56 (dd, 1 H, J = 4.1, 9.0 Hz, Ar: 6-H), 7.87 (dd, 1 H, J = 2.6, 9.1 Hz, Ar: 4-H), 8.14 (s, 1 H, Ar: 2-H), 8.20 (d, 1 H, J = 14.2 Hz, NCH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.53 (q), 51.86 (q), 104.49 (d), 107.92 (dd), 111.16 (dd), 112.99 (dd), 127.95 (d, C-F), 130.46 (d), 132.66 (s), 136.29 (d), 158.80 (s), 161.19 (s), 163.97 (s), 166.72 (s); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −5.41 (s); IR (KBr) 3114 (w), 3082 (w, ArH), 2950 (w), 2925 (m), 2850 (w), 1706 (s, C=O), 1646 (s, C=O), 1552 (s, C=C), 1478 (s, CH), 1434 (s, CH), 1380 (s), 1230 (s), 1171 (s), 989 (m), 890 (m), 859 (m), 811 (m), 780 (m), 766 (m) cm^{-1}; MS m/e (relative intensity) 277 (M^+, 64.9), 246 (65.5), 213 (18.6), 185 (15.9), 129 (45.9), 73 (100); exact mass calcd for $C_{14}H_{12}NO_4F$ 277.0750, found 277.0736. Anal. Calcd for $C_{14}H_{12}NO_4F$: C, 60.65; H, 4.36; N, 5.05. Found: C, 60.28; H, 4.33; N, 5.02.

1-[2-(Methoxycarbonyl)vinyl]-6-(trifluoromethyl)-1*H*-indole-3-carboxylic Acid Methyl Ester (5n). The standard procedure was followed by use of *N*-[3-(α,α,α-trifluoromethyl)-phenyl]hydroxylamine (49.8 mg, 0.281 mmol, 1.0 equiv), THF (6.0 mL), 4A molecular sieves (0.51 g), DMAP (4.3 mg, 0.035 mmol), and methyl propiolate (0.10 mL, 94.5 mg, 1.12 mmol, 4.0 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5n** as a white solid in 52% yield (47.7 mg, 0.146 mmol): mp 177.0–178.5 °C; TLC R_f 0.25 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 4.42 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 6.24 (d, 1 H, J = 14.2 Hz, NC=CH), 7.65 (d, 1 H, J = 8.3 Hz, Ar: 5-H), 7.91 (s, 1 H, Ar: 7-H), 8.25 (s, 1 H, Ar: 2-H), 8.28 (d, 1 H, J = 14.2 Hz, NCH=), 8.34 (d, 1 H, J = 8.3 Hz, Ar: 4-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.70 (q), 52.03 (q), 105.60 (d), 107.82 (d), 113.13 (s), 120.58 (d), 123.02 (d), 125.73 (s), 127.09 (q, CF_3), 129.51 (s), 131.28 (d), 135.53 (s), 135.69 (d), 163.81 (s), 166.45 (s); ^{19}F NMR ($CDCl_3$, 282 MHz) δ 51.97 (s); IR (KBr) 3122 (m), 3073 (w, ArH), 2958 (w), 1716 (s, C=O), 1646 (s, C=O), 1546 (s, C=C), 1444 (s, CH), 1374 (m), 1342 (s), 1223 (s), 1158 (s), 1040 (s), 949 (s), 865 (s), 832 (s), 772 (s) cm^{-1}; MS m/e (relative intensity) 327 (M^+, 100), 308 (7.4), 296 (99), 264 (11.3), 252 (12.8), 237 (9.4), 212 (8.4), 183 (6.4), 132 (7.4), 107 (7.4); exact mass calcd for $C_{15}H_{12}NO_4F_3$ 327.0718, found 327.0724. Anal. Calcd for $C_{15}H_{12}NO_4F_3$: C, 55.05; H, 3.70; N, 4.28. Found: C, 54.72; H, 3.65; N, 4.18.

4-(Dimethylamino)-1-[(2-methoxycarbonyl)vinyl]-1*H*-indole-3-carboxylic Acid Methyl Ester (5o) and 6-(Dimethylamino)-1-[(2-methoxycarbonyl)vinyl]-1*H*-indole-3-carboxylic Acid Methyl Ester. The standard procedure was followed by use of *N*-[3-(dimethylamino)phenyl]hydroxylamine (49.6 mg, 0.326 mmol, 1.0 equiv), THF (20.0 mL), 4A molecular sieves (0.48 g), DMAP (4.0 mg, 0.033 mmol), and methyl propiolate (113.4 mg, 1.31 mmol, 4.0 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5o** and its isomer with the NMe_2 group at the C-6 position as yellow solids in 61% overall yield (59.8 mg, 0.198 mmol).

The major isomer **5o** was separated by recrystallization with 20% EtOAc in hexanes. For **5o**: mp 131.5–132.5 °C; TLC R_f 0.20 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 9.11 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (s, 6 H, $N(CH_3)_2$), 3.80 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.07 (d, 1 H, J = 14.1 Hz, NC=CH), 6.81 (d, 1 H, J = 7.9 Hz, Ar: 5-H), 7.16 (d, 1 H, J = 7.9 Hz, Ar: 7-H), 7.25–7.30 (m, 1 H, Ar: 6-H), 7.95 (s, 1 H, Ar: 2-H), 8.22 (d, 1 H, J = 14.1 Hz, NCH=); IR (KBr) 3112 (m), 2952 (m), 2840 (w), 1715 (s, C=O), 1641 (s, C=O), 1578 (s, C=C), 1535 (s), 1497 (s), 1452 (s, CH), 1432 (s, CH), 1373 (s), 1356 (s), 1321 (s), 1291 (s), 1213 (s), 1192 (s), 1175 (s), 1150 (s), 1041 (s), 961 (m), 854 (m) cm^{-1}; MS m/e (relative intensity) 302 (M^+, 47), 287 (41.7) 274 (12.4), 269 (16.7), 255 (100), 241 (5.8), 196 (5.9), 170 (5.8), 135 (8.6), 115 (3.8), 92 (3.7); exact mass calcd for $C_{16}H_{18}N_2O_4$ 302.1266, found 302.1247. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.32; H, 6.00; N, 9.17.

For its isomer with the NMe_2 group at the C-6 position: mp 186–187 °C; TLC R_f 0.20 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 13.16 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.05 (s, 6 H, $N(CH_3)_2$), 3.83 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.06 (d, 1 H, J = 14.1 Hz, NC=CH), 6.76 (s, 1 H, Ar: 7-H), 6.87 (d, 1 H, J = 8.9 Hz, Ar: 5-H), 7.88 (s, 1 H, Ar: 2-H), 7.96 (d, 1 H, J = 8.9 Hz, Ar: 4-H), 8.23 (d, 1 H, J = 14.1 Hz, NCH=); IR (KBr) 3131 (w), 2954 (w), 1710 (s, C=O), 1639 (s, C=O), 1630 (s), 1554 (s, C=C), 1511 (m), 1436 (w, CH), 1410 (w, CH), 1373 (w), 1342 (w), 1254 (s), 1229 (m), 1167 (s), 1132 (s), 955 (w) cm^{-1}; MS m/e (relative intensity) 302 (M^+, 100), 287 (3.4), 269 (12.9),

255 (5.4), 243 (4.8), 228 (8.5), 196 (4.4), 185 (4.1), 135 (5.8), 119 (7.5), 106 (3.7); exact mass calcd for $C_{16}H_{18}N_2O_4$ 302.1266, found 302.1260. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.15; H, 5.95; N, 9.17.

7-(Trifluoromethyl)-1*H*-indole-3-carboxylic Acid Methyl Ester (5p). The standard procedure was followed by use of *N*-[2-(α,α,α-trifluoromethyl)phenyl]hydroxylamine (58.2 mg, 0.329 mmol, 1.0 equiv), THF (6.0 mL), 4A molecular sieves (0.60 g), DMAP (6.0 mg, 0.049 mmol), and methyl propiolate (66.2 mg, 0.79 mmol, 2.4 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5p** as a white solid in 78% yield (62.4 mg, 0.257 mmol): mp 162.5–163.5 °C; TLC R_f 0.30 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) to t_R 2.13 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 3 H, OCH_3), 7.30–7.36 (m, 1 H, Ar: 5-H), 7.52 (d, 1 H, J = 7.6 Hz, Ar: 6-H), 7.99 (d, 1 H, J = 3.0 Hz, Ar: 2-H), 8.39 (d, 1 H, J = 8.2 Hz, Ar: 4-H), 9.09 (br, s, 1 H, NH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −5.41 (s); IR (KBr) 3292 (br, s, NH), 3136 (w), 2992 (w), 2960 (m), 1701 (s, C=O), 1541 (s, C=C), 1443 (s, CH), 1359 (s), 1316 (s), 1127 (br, s), 965 (s), 900 (s), 854 (m), 799 (s), 705 (s) cm^{-1}; MS m/e (relative intensity) 243 (M^+, 83.3), 224 (9.0), 212 (99), 192 (100), 164 (10), 144 (18.5), 96 (10); exact mass calcd for $C_{11}H_8NO_2F_3$ 243.0507, found 243.0509. Anal. Calcd for $C_{11}H_8NO_2F_3$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.19; H, 3.32; N, 5.71.

1-[2-(Methoxycarbonyl)vinyl]-1*H*-indole-3-carboxylic Acid Methyl Ester (5q). The standard procedure was followed by use of *N*-(2-methoxyphenyl)hydroxylamine (128.0 mg, 0.921 mmol, 1.0 equiv), THF (7.0 mL), 4A molecular sieves (1.27 g), DMAP (11.4 mg, 0.093 mmol), and methyl propiolate (311.9 mg, 3.71 mmol, 4.0 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5q** as a white solid in 62% yield (146.8 mg, 0.567 mmol): mp 149–150 °C; TLC R_f 0.28 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 5.60 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.15 (d, 1 H, J = 14.0 Hz, NC=CH), 7.31–7.44 (m, 2 H, Ar: 5-H, 6-H), 7.62 (d, 1 H, J = 8.1 Hz, Ar: 7-H), 8.10 (s, 1 H, Ar: 2-H), 8.19 (d, 1 H, J = 8.1 Hz, Ar: 4-H), 8.26 (d, 1 H, J = 14 Hz, NCH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.36 (q), 51.71 (q), 103.84 (d), 110.09 (d), 113.11 (s), 122.12 (d), 123.76 (d), 124.64 (d), 126.94 (s), 129.17 (d), 136.26 (s), 136.32 (d), 164.24 (s), 166.83 (s); IR (KBr) 3118 (m), 3076 (m, ArH), 2947 (m), 1707 (s, C=O), 1639 (s, C=O), 1549 (s, C=C), 1467 (s, CH), 1438 (s, CH), 1377 (s), 1303 (s), 1261 (s), 1226 (s), 1167 (s), 976 (s), 852 (s), 776 (s), 744 (s) cm^{-1}; MS m/e (relative intensity) 259 (M^+, 100), 228 (89.1), 196 (6.1), 185 (16.1), 169 (10.2), 140 (9.1), 114 (6.9), 98 (13.1), 44 (14.13); exact mass calcd for $C_{14}H_{13}NO_4$ 259.0844, found 259.0848. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.49; H, 4.68; N, 5.24.

6-Ethoxy-1-[2-(methoxycarbonyl)vinyl]-1*H*-indole-3-carboxylic Acid Methyl Ester (5r). The standard procedure was followed by use of *N*-(2,5-diethoxyphenyl)hydroxylamine (32.2 mg, 0.163 mmol, 1.0 equiv), THF (6.0 mL), 4A molecular sieves (0.30 g), DMAP (2.6 mg, 0.021 mmol), and methyl propiolate (57.6 mg, 0.67 mmol, 4.2 equiv). After 48 h, the reaction was worked up, and the residue was purified by use of a chromatotron to give **5r** as a pink solid in 45% yield (79.0 mg, 0.275 mmol): mp 150–151 °C; TLC R_f 0.30 (20% EtOAc in hexanes as eluant); GC (isothermal 250 °C) t_R 9.43 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (t, 3 H, J = 7.0 Hz, CH_3), 3.82 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.10 (q, 2 H, J = 7.0 Hz, CH_2), 6.08 (d, 1 H, J = 14.0 Hz, NC=CH), 6.97 (d, 1 H, J = 8.7 Hz, Ar: 5-H), 7.02 (s, 1 H, Ar: 7-H), 7.95 (s, 1 H, Ar: 2-H), 8.01 (d, 1 H, J = 8.7 Hz, Ar: 4-H), 8.17 (d, 1 H, J = 14.0 Hz, NCH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.78 (q), 51.39 (q), 51.76 (q), 64.04 (t), 94.92 (d), 103.46 (d), 113.32 (s), 113.47 (d), 120.68 (s), 122.74 (d), 127.89 (d), 136.38 (d), 137.38 (s), 157.50 (s), 164.40 (s), 167.03 (s); IR (KBr) 3117 (w), 3068 (w, Ar-H), 2977 (w), 2950 (m), 1712 (s, C=O), 1650 (s, C=O), 1549 (s, C=C), 1496 (m), 1257 (s), 1207 (s), 1120 (m), 1090 (m), 1045 (s), 951 (s), 818 (s), 766 (m) cm^{-1}; MS m/e (relative intensity) 303 (M^+, 100), 274 (54.5), 272 (17.8), 244 (26.2), 200 (5.9), 185 (6.9), 172 (4.0), 156 (6.4); exact mass calcd for $C_{16}H_{17}NO_5$ 303.1107, found 303.1103. Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 62.89; H, 5.64; N, 4.56.

Enamine *N*-Oxide Intermediate 9. To a solution of *N*-benzyl-*N*-phenylhydroxylamine (112 mg, 0.553 mmol, 1.0 equiv) in MeOH (15 mL) was added methyl propiolate (70.0 mg, 0.731 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for an additional 1 h and at room temperature for 50 h. After the solvent was removed under reduced pressure, the resultant oil was purified by use of flash column chromatography over silica gel with EtOAc/hexanes = 3/7 as the eluant to give **9** (contaminated with a trace of **5a**) as an oil (47.6 mg): TLC R_f 0.15 (10% EtOAc in hexanes as eluant); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3 H, OCH_3), 4.91 (s, 2 H, CH_2Ph), 5.43 (d, 1 H, J = 12.5 Hz, N^+C=CH), 7.11–7.45 (m, 10 H, ArH), 7.95 (d, 1 H, J = 12.5 Hz, N^+CH=C); MS m/e (relative intensity) 267 ($M^{\bullet+}$ − 16, 32), 252 (5.4), 236 (9.2), 208 (21), 193 (6.6), 176 (5.1), 144 (3.4), 104 (12), 91 (100), 77 (15), 65 (11).

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