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Friedel–Crafts addition of indoles to nitrones promoted by trimethylsilyl trifluoromethanesulfonate

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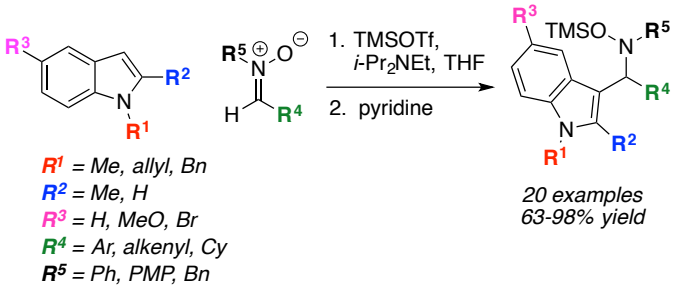
ABSTRACT

N-alkylindoles undergo Friedel–Crafts addition to aryl and secondary alkyl nitrones in the presence of trimethylsilyl trifluoromethanesulfonate and a trialkylamine to produce 3-(1-(silyloxyamino)alkyl)indoles. Spontaneous conversion to the bisindolyl(aryl)methanes, which is thermodynamically favored for nitrones derived from aromatic aldehydes, is suppressed under the reaction conditions. The silyloxyamino group can be deprotected with tetrabutylammonium fluoride to yield the hydroxylamine.



The aminoalkylation of indoles via Friedel–Crafts addition to imines is well established,[1,2] providing 1:1 indole:imine adducts in high yield.[3] Additions to the related nitrone electrophiles to provide the analogous 1:1 indole:nitrone adducts, however, are almost unknown. While a seminal report by Vallée and colleagues showed that 1:1 adducts **1** can be constructed from *N*-benzylnitrones derived from unbranched aliphatic aldehydes (e.g., acetaldehyde, propionaldehyde), nitrones derived from benzaldehyde and isobutyraldehyde did not provide the desired products (Fig 1).[4] Instead, bisindolyl product **2a** was formed, which likely derives from the ionization of product **1** through the loss of the hydroxylamino group followed by nucleophilic attack by a second equivalent of indole.[5] The generation of this thermodynamically favored 2:1 adduct has also been observed when indoles are treated with aromatic aldehydes, as noted by Fischer as early as the 19th century.[6] Vallée, et al., report only a single exception to this trend, the addition of indole to a nitrone derived from the electron-deficient 4-nitrobenzaldehyde, which

proceeded in 44% yield. Few alternatives exist for the generation of this class of products, and these non-Friedel–Crafts routes are extremely limited in terms of substrate scope.[7] Here, we describe a solution to this problem, the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-promoted Friedel–Crafts addition of *N*-alkylated indoles to nitrones derived from aromatic, alkenyl, and branched aliphatic aldehydes to yield 1:1 indole:nitrone adducts.

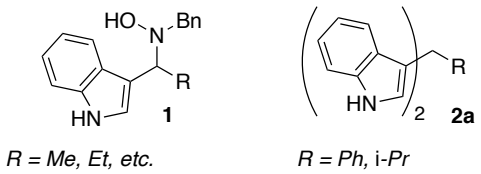
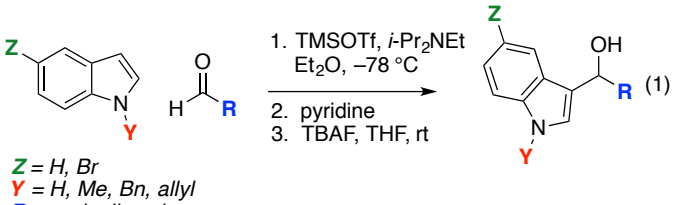
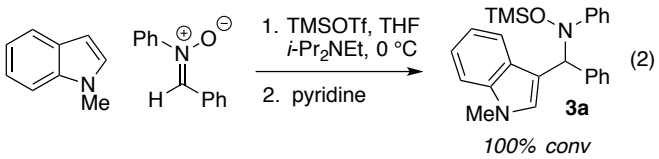


Figure 1. The 1:1 and 2:1 indole-nitrone adducts observed by Vallée, et al.

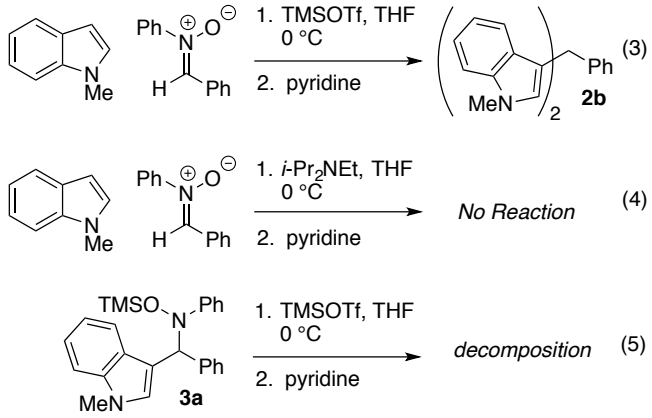
We recently reported the generation of 1:1 indole:aldehyde adducts through a Friedel–Crafts pathway promoted by TMSOTf and *i*-Pr_2NEt (eq 1),[8] a process amenable to aryl aldehydes that normally undergo rapid conversion to 2:1 adducts **2** under Lewis acidic conditions.[9] Encouraged by this suppression of the thermodynamically favored 2:1 adduct, we turned to the challenging nitrone electrophiles, for which our group has developed a number of TMSOTf-promoted methods.[10] To begin, the addition of *N*-methylindole to *N*,α-diphenylnitrone in the presence of TMSOTf and *i*-Pr_2NEt in a variety of reaction solvents was assessed. When methylene chloride was employed as solvent, formation of the undesired 2:1 product competed with the desired reaction. Other solvents (diethyl ether, cyclopentyl methyl ether, toluene), however, promoted the desired selectivity for the 1:1 adduct, and THF was notably superior, providing full conversion to the 1:1 adduct in one hour at –78 °C. After optimization, this reaction could be performed conveniently at 0 °C without detectable generation of undesired byproducts by employing small excesses of the nitrone (1.1 equiv), TMSOTf (1.2 equiv), and *i*-Pr_2NEt (1.3 equiv) (eq 2). Even under optimized conditions, replacement of TMSOTf with a number of other promoters ($Zn(OTf)_2$, $Fe(OTf)_3$, HCl, TMSCl), both with and without amine base, provided only the undesired 2:1 products, which suggests that silyl triflates may be uniquely effective in this transformation.[11]





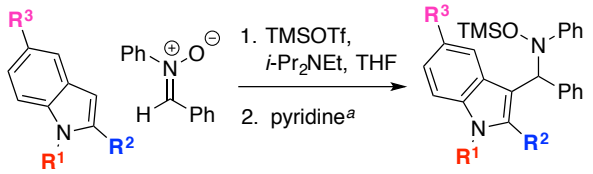
Despite their observed stability under the reaction conditions, the desired product did show some acid sensitivity, even when purified. For example, some decomposition was observed when a purified reaction product was allowed to stand in deuterated chloroform for three hours; therefore, deuterated methylene chloride was employed for all other NMR experiments, including characterization. Out of an abundance of caution, and in analogy to our method for the Friedel–Crafts addition of indoles to aldehydes,[8] all unpurified reaction mixtures were quenched prior to workup by the addition of pyridine, a procedure that presumably sequesters any remnants of TMSOTf and prevents Lewis acid-catalyzed conversion to the 2:1 adduct.[12]

In order to verify the importance of each component of the reaction mixture, a series of control experiments was performed. When the reaction was attempted in the absence of *i*-Pr_2NEt, only the 2:1 adduct was observed (eq 3). In contrast, removal of TMSOTf from the reaction mixture resulted in no reaction at all, and the indole and nitrone were recovered unchanged (eq 4). Finally, when product **3a** was subjected to TMSOTf alone, decomposition was observed and no recognizable products were recovered (eq 5). Based on these observations, we hypothesize that the *i*-Pr_2NEt, in addition to serving as a Brønsted base, acts to buffer the Lewis acidity of the TMSOTf, an interaction that suppresses Lewis acid-catalyzed ionization and decomposition of the desired product.



With the optimized reaction conditions in hand, a number of indoles were tested for efficacy (Table 1). The standard *N*-methylindole substrate reacted with excellent efficiency when treated with *N*,α-diphenylnitrone, providing the silyloxyamino product in 93% yield (entry 1). Production of this adduct could be accomplished with full conversion even at –78 °C, and removal of the TMS group under suitably basic conditions (TBAF, THF, –20 °C) provided the hydroxylamine in 82% overall yield (entry 2). Other representative indoles, including 5-substituted indoles and the conveniently protected *N*-benzyl and *N*-allyl variants, provided similar yields (entries 3-7).

Table 1. Addition of various indoles to *N*,α-diphenylnitrone

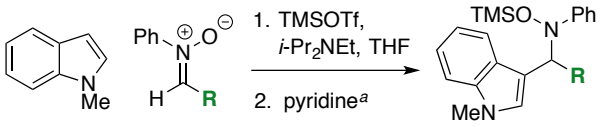


entry	R^1	R^2	R^3	*t* (h)	product	yield (%)[b]
1	Me	H	H	0.5	**3a**	93
2	Me	H	H	2	**3b**	82[c]
3	Me	Me	H	0.5	**4**	85
4	Me	H	Br	0.5	**5**	93
5	Me	H	MeO	0.5	**6**	96
6	allyl	H	H	0.5	**7**	74
7	Bn	H	H	1	**8**	69[c]

[a]Reaction conditions: 1) 1.0 mmol *N*-methylindole, 1.1 mmol nitrone, 1.2 mmol TMSOTf, 1.3 mmol *i*-Pr_2NEt, 5 mL THF; 2) 2.6 mmol pyridine. [b]Isolated yield after chromatography. [c]Reaction performed at –78 °C. Yield is for desilylated product. Reaction conditions for deprotection: 1.1 mmol TBAF, 10 mL THF, –20 °C, 10 min.

A survey of the addition of *N*-methylindole to various *N*-phenylnitrones followed (Table 2). Although a search of the literature revealed only a single isolated example of the Friedel–Crafts addition of an indole to an α-arylnitrone to yield a 1:1 adduct,[4] our system showed great generality in this regard. The 4-nitrobenzaldehyde derivative underwent reaction in 82% yield (entry 1), a marked improvement over the lone successful example of such a reaction in the literature, which employed the same nitrone, albeit in reaction with free indole.[4] Strikingly, other benzaldehyde derivatives were also strong substrates (entries 2-6), including both electron-poor and the challenging electron-rich examples. Heteroaromatic and alkenyl substrates also reacted in good yield (entries 7-9), as did the branched-alkyl nitrone derived from cyclohexanecarboxaldehyde (entry 10). Entries 2-10 provide a complement to previous reports in the literature and, to the best of our knowledge, illustrate a series of unprecedented results.

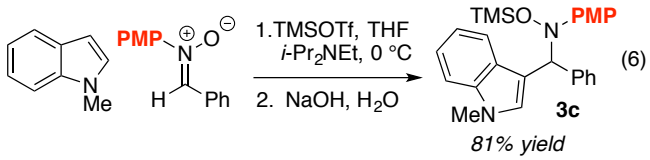
Table 2. Addition of *N*-methylindole to various nitrones

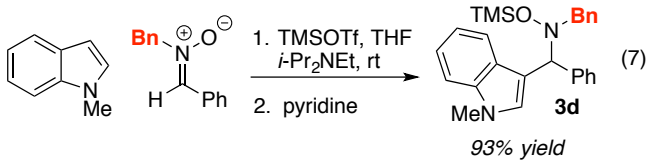


entry	R	T (°C)	*t* (h)	product	yield (%)[b]
1	4-(NO_2)Ph	–78	3	**9**	82
2	4-FPh	–78	3	**10**	69
3	4-BrPh	–78	3	**11**	70
4	4-MePh	–78	3	**12**	94
5	4-MeOPh	0	1	**13**	74
6	2-naphthyl	–78	3	**14**	94
7	2-furyl	0	0.5	**15**	94[c]
8	2-thienyl	0	3	**16**	77
9	cinnamyl	0	0.5	**17**	63
10	Cy	0	3	**18**	85

[a]Reaction conditions: 1) 1.0 mmol *N*-methylindole, 1.1 mmol nitrone, 1.2 mmol TMSOTf, 1.3 mmol *i*-Pr_2NEt, 5 mL THF; 2) 2.6 mmol pyridine. [b]Isolated yield after chromatography. [c]Reaction performed on a 0.75 mmol scale in 8.0 mL THF.

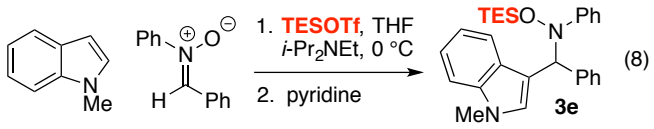
Nitrones featuring *N*-protecting groups other than phenyl reacted with a range of results. For example, *N-tert*-butyl-α-phenylnitrone provided only the bisindolyl 2:1 adduct, while *N*-methyl-α-phenylnitrone did not appear to react at all. In contrast, the conveniently protected *N-para*-methoxyphenyl (PMP)-protected nitrone reacted smoothly to provide the product in 81% yield (eq 6). Unlike its *N*-phenyl analogs, however, this adduct required basic aqueous extraction prior to chromatography in order to isolate the product in high yield without decomposition. When a benzyl-protected nitrone was employed, reactivity slowed considerably, requiring two hours at room temperature to reach full conversion, but high yield was attained again (eq 7).





Next, other trialkylsilyl trifluoromethanesulfonates were tested as replacements for TMSOTf. The triethylsilyl-protected product **3e** was isolated in 98% yield when TMSOTf was replaced with triethylsilyl trifluoromethanesulfonate (TESOTf) under otherwise identical reaction conditions (eq 8). When *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) was employed, however, only the undesired 2:1 product was observed. This result, when combined with the earlier observation that

employment of *N*-*tert*-butyl-α-phenyl nitrone also led to the 2:1 adduct, suggests that bulkier groups attached to the amine residue (e.g., *tert*-butyl, *tert*-butyldimethylsilyloxy) may promote ionization of the desired product in order to relieve steric congestion.

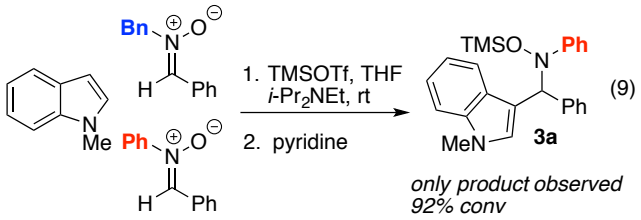


(8)

98% yield

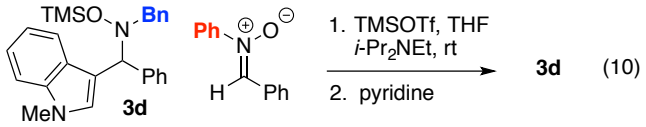
Despite the wide reaction scope and the stability of the products under the reaction conditions, purification of the desired products was, in several cases, impeded by decomposition during chromatography. Although electron-poor and desilylated products were amenable to standard silica gel chromatography with ethyl acetate and hexane, for silylated products **3a**, **3e**, **4** - **7**, **13**, and **15**, it was necessary to replace silica gel with neutral alumina and dope the ethyl acetate/hexane solvent system with 1% diethylamine to suppress decomposition. These modified chromatography conditions were found to be reliable and reproducible, and became the purification method of choice as the study progressed. Prior to the development of these conditions, however, a variety of other chromatography conditions were employed. Some reactions provided the desired product in high purity after rapid filtration through a short plug of silica with diethyl ether (products **12**, **14**), while other products could be purified by chromatography on basic alumina (products **16**, **17**). Still other products were isolated after silica gel chromatography with 1% diethylamine was included as a coeluent (products **3c**, **3d**, and **18**).

With the reaction scope established, a series of experiments was conducted in order to test the reversibility of the reaction under typical conditions. First, a competition experiment was performed wherein *N*-methylindole was treated simultaneously with both N-benzyl and N-phenyl nitrones (1.4 equiv each), as well as TMSOTf and *i*-Pr_2NEt, at room temperature for 30 min (eq 9). Analysis of the unpurified reaction mixture revealed 100% selectivity for the formation of N-phenyl product **3a** over the formation of the N-benzyl product, even at high conversion. Next, a crossover experiment was performed wherein N-benzyl product **3d** was treated with *N*,α-diphenylnitrone under the same reaction conditions. In this case, original product **3d** was recovered unchanged, and no trace of N-phenyl product **3a** was observed (eq 10). Because the faster-forming N-phenyl product **3a** was not observed under conditions where it is known to react rapidly with *N*-methylindole, these data suggest that there is no appreciable reversion of product **3d** to the original indole, and therefore the silylative Friedel–Crafts addition is effectively *not reversible* under the reaction conditions.



(9)

only product observed
92% conv



(10)

The scope of this reaction appears to be limited to N-alkylated indoles at present. When the unprotected free indole was tested, it underwent non-quantitative *N*-silylation under the reaction conditions, which complicated reproducibility and isolation of the desired product. Indole analogs benzofuran and thianaphthene were completely unreactive under our optimized conditions, and failed to react even at elevated temperatures. Finally, it should be noted that when the nitrone was replaced with the dimethyl acetals of propionaldehyde or acetaldehyde, a reaction did occur but only the 2:1 adduct was generated, a transformation already well established in the literature under other conditions.[13]

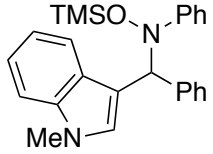
In summary, we have described the Friedel–Crafts (silyloxy)aminoalkylation of indoles with nitrones derived from aromatic, alkenyl, and α-branched aliphatic aldehydes, a substrate scope that complements previous reports in the literature. The reaction relies upon a buffered *i*-Pr_2NEt–TMSOTf system to prevent conversion to the 2:1 bisindolyl product, which otherwise acts as a thermodynamic sink under acidic conditions. The products can be isolated as either the silylated 1:1 adducts or the corresponding deprotected hydroxylamines.

EXPERIMENTAL SECTION

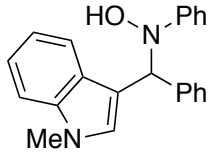
General. Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF) was purified by passage through a bed of activated alumina.[14] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylsilyl trifluoromethanesulfonate (TESOTf) were stored in Schlenk flasks under inert atmosphere. Hunig's base (*i*-Pr_2NEt) was distilled from calcium hydride and stored in a Schlenk flask under inert atmosphere. *N*-Methylindole was passed through a plug of silica with ether and concentrated in vacuo. Other indoles were prepared by treatment of indole with sodium hydride and the corresponding alkyl bromide (*N*-allylindole, *N*-benzylindole) or iodide (5-methoxy-*N*-methylindole) or were used as received. Nitrones were used as received (*N*,α-diphenylnitrone, *N*-*tert*-butyl-α-phenylnitrone) or were prepared via literature precedent.[15] All other chemicals were used as received. Purification of reaction products was carried out by flash chromatography using silica gel (230-400 mesh), neutral alumina (activated, Brockmann I, 120 mesh), or basic alumina (activated, Brockmann I, 60 mesh). Analytical thin layer chromatography was performed on silica gel plates. Visualization was accomplished with UV light and phosphomolybdic acid stain, followed by heating. Infrared spectra were recorded on an FT-IR spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz spectrometer, 400 MHz spectrometer, or 300 MHz spectrometer, and are reported in ppm using solvent as an internal standard (CD_2Cl_2 at 5.32 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, sp=septet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C NMR spectra were recorded on a 125 MHz spectrometer, 100 MHz spectrometer, or 75 MHz spectrometer, and are reported in ppm using solvent as an internal standard (CD_2Cl_2 at 53.8 ppm). High-resolution mass

spectra were obtained by electrospray ionization unless otherwise indicated. Melting points were determined using a capillary melting point apparatus.

General Procedure. *Addition of indoles to nitrones*
To an oven-dried round-bottomed flask under N_2 atmosphere were added the nitrone (1.10 mmol), tetrahydrofuran (THF, 2.5 mL), indole (1.00 mmol), and *i*-Pr_2NEt (226 μL, 168 mg, 1.30 mmol). The mixture was cooled to the appropriate reaction temperature, and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 217 μL, 266 mg, 1.20 mmol) was added dropwise. The mixture was stirred for the designated time, then treated with pyridine (210 μL, 205 mg, 2.60 mmol). The mixture was quickly passed through a column of silica (4 cm x 1 cm) with Et_2O (20 mL). The solvent was removed in vacuo, and the residue purified by column chromatography.

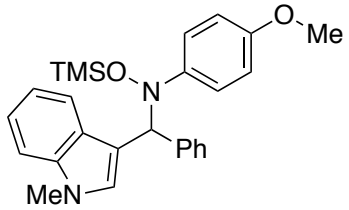


***N*-((1-Methyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (3a)** The title compound[16] was prepared according to the General Procedure at 0 °C for 30 min reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (217 mg, 1.10 mmol). Purification by column chromatography on neutral alumina (0-1% EtOAc/hexanes doped with 1% diethylamine) provided the as a sticky yellow solid (373 mg, 93% yield): IR (film) 3062, 3031, 2955, 2900, 1596, 1486, 1451, 1260, 1249, 1207, 1013, 887, 838, 736 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 6.8 Hz, 2H), 7.36 – 7.23 (m, 6H), 7.23 – 7.16 (m, 4H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 7.2 1H), 6.00 (s, 1H), 3.77 (s, 3H), -0.17 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 155.1, 142.4, 138.5, 131.9, 131.6, 130.1, 129.9, 129.6, 129.0, 124.4, 123.2, 121.44, 121.36, 120.8, 113.9, 111.0, 72.2, 34.5, 0.9; Accurate mass for product **3a** could not be detected because of rapid fragmentation (loss of (TMSO)NPh) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{25}H_{27}N_2OSi$ $[M–H]^+$, 399.1887; found, 399.1890.

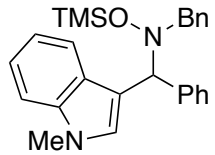


***N*-((1-Methyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenylhydroxylamine (3b)** The title compound[16] was prepared according to a variation of the General Procedure at –78 °C for a 2 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (217 mg, 1.10 mmol). The unpurified product that resulted from the General Procedure was dissolved in THF (10 mL) and cooled to –20 °C, then treated with tetrabutylammonium fluoride (1100 μL, 1.0 M in THF, 1.10 mmol). After 10 min, the

reaction mixture was partitioned between saturated $NaHCO_3$ (50 mL) and Et_2O (50 mL). The layers were separated, and the organic layer was diluted with hexanes (150 mL) and dried over Na_2SO_4. The solids were removed by filtration and the solvent removed in vacuo. The residue was purified by column chromatography (5 – 10% EtOAc/hexanes on silica gel). The product was isolated as a foamy yellow solid (282 mg, 86% yield): mp: 40-44 °C; IR (film) 3490, 3056, 3026, 1598, 1487, 1331, 1229, 1015, 737, 694 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.63 (dd, J = 23.6, 7.9 Hz, 3H), 7.51 – 7.27 (m, 9H), 7.19 – 6.98 (m, 3H), 6.34 (s, 1H), 5.45 (bs, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 151.8, 140.5, 137.1, 129.7, 129.0, 128.6, 128.2, 127.7, 127.2, 121.7, 121.6, 119.8, 119.2, 117.0, 112.3, 109.4, 66.9, 32.7; HRMS (ESI, TOF): Exact mass calcd for $C_{22}H_{19}N_2O$ $[M–H]^+$, 327.1492; found, 327.1495.

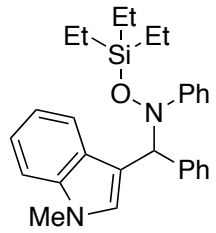


***N*-(4-Methoxyphenyl)-*N*-((1-methyl-1*H*-indol-3-yl)(phenyl)methyl)-*O*-(trimethylsilyl)hydroxylamine (3c)** The title compound[16] was prepared according to a variation of the General Procedure at 0 °C for a 0.5 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*Z*)-*N*-(4-methoxyphenyl)-1-phenylmethanimine oxide (250 mg, 1.10 mmol) as the nitrone. Purification of this compound required a different workup from the general procedure: Upon completion of the reaction time, no pyridine was added. Instead, the reaction mixture was diluted with 1.0 N NaOH (20 mL) and diethyl ether (20 mL). The layers were separated and the aqueous layer was back-extracted with diethyl ether (20 mL). The combined organic layers were dried with Na_2SO_4, then the solids were removed by gravity filtration and the solvents removed in vacuo. Column chromatography on silica gel (1-5% EtOAc/hexanes doped with 1% diethylamine) provided the product as a yellow foam (348 mg, 81% yield): mp: 50 – 52 °C; IR (film) 3062, 2959, 2900, 2832, 1502, 1465, 1244, 1204, 1034, 925, 887, 837, 737, 701 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.79 (d, J = 8.0 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.46 – 7.24 (m, 6H), 7.21 – 7.12 (m, 2H), 6.81 – 6.75 (m, 2H), 5.89 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), -0.07 (d, J = 0.7 Hz, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 157.8, 148.3, 142.8, 138.5, 131.7, 131.4, 130.0, 129.5, 128.8, 124.0, 123.1, 121.7, 120.6, 114.8, 114.5, 110.9, 73.0, 57.0, 34.5, 0.9; HRMS (ESI, TOF): Exact mass calcd for $C_{26}H_{29}N_2O_2Si$ $[M–H]^+$, 429.1993; found, 429.1973.

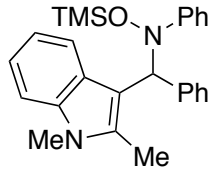


***N*-Benzyl-*N*-((1-methyl-1H-indol-3-yl)(phenyl)methyl)-*O*-(trimethylsilyl)hydroxylamine (3d)** The title compound[16] was prepared according to the

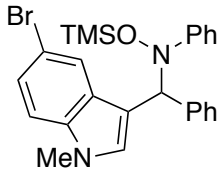
General Procedure at room temperature for a 2 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*Z*)-*N*-benzyl-1-phenylmethanimine oxide (211 mg, 1.00 mmol). Purification by column chromatography on silica gel (1-2% EtOAc/hexanes doped with 1% diethylamine) provided the as a sticky white solid (387 mg, 93% yield): IR (film) 3289, 3064, 3030, 2956, 2904, 1682, 1488, 1453, 1246, 922, 896, 836, 751, 737, 698 cm^{-1}; NMR analysis at ambient temperature was complicated by evidence of conformational isomers. Reported NMR data were observed at 315 K: ^1H NMR (500 MHz, CD_2Cl_2) δ 7.82 – 7.65 (m, 3H), 7.47 – 7.42 (m, 7H), 7.41 – 7.37 (m, 2H), 7.36 – 7.32 (m, 1H), 7.27 (bs, 1H), 7.24 – 7.19 (m, 1H), 5.46 (s, 1H), 4.20 – 3.91 (m, 2H), 3.87 (s, 3H), -0.15 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 142.5, 139.3, 137.9, 131.2, 130.5, 129.9, 129.0, 128.8, 128.7, 127.9, 127.8, 122.3, 121.2, 119.7, 113.8, 109.9, 68.9, 63.2, 33.3, 0.2.; Accurate mass for product **3d** could not be detected because of rapid fragmentation (loss of (TMSO)NBn) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{23}H_{21}N_2O$ $[M–H]^+$, 341.1648; found, 341.1632.



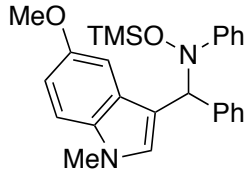
***N*-((1-Methyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenyl-*O*-(triethylsilyl)hydroxylamine (3e)** The title compound[16] was prepared according to the General Procedure at 0 °C for 30 min reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (217 mg, 1.10 mmol). Purification by column chromatography on neutral alumina (0-1% EtOAc/hexanes doped with 1% diethylamine) provided the product as a sticky yellow-orange solid (432 mg, 98% yield): IR (film) 2952, 2911, 2875, 1595, 1484, 1451, 1412, 1375, 1233, 1206, 1062, 1013, 953, 915, 877, 762, 734, 695 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.65 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.4 Hz, 2H), 7.34 – 7.25 (m, 4H), 7.24 – 7.18 (m, 3H), 7.19 – 7.11 (m, 2H), 7.10 – 7.02 (m, 2H), 6.93 (t, J = 7.2 Hz, 1H), 5.89 (s, 1H), 3.75 (s, 3H), 0.78 (t, J = 7.9 Hz, 9H), 0.35 (q, J = 7.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 153.6, 140.5, 136.8, 130.1, 129.9, 128.4, 127.9, 127.8, 127.2, 123.2, 121.5, 120.6, 119.8, 119.0, 112.3, 109.2, 71.4, 32.7, 6.8, 4.3; Accurate mass for product **3e** could not be detected because of rapid fragmentation (loss of (TESO)NPh) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{22}H_{19}N_2O$ $[M–H]^+$, 327.1492; found, 327.1499.



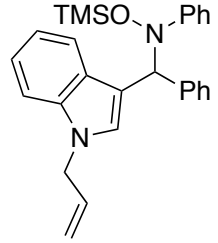
***N*-((1,2-Dimethyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (4)** The title compound[16] was prepared according to the General Procedure at 0 °C for 30 min reaction time, using 1,2-dimethylindole (145 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (217 mg, 1.10 mmol). Purification by column chromatography on neutral alumina (0-1% EtOAc/hexanes doped with 1% diethylamine) provided the as a sticky yellow foam (352 mg, 85% yield): IR (film) 3058, 3031, 2955, 2915, 2849, 1595, 1487, 1470, 1450, 1406, 1367, 12348, 1177, 1132, 1052, 1022, 913, 876, 838, 727, 695 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.79 (d, J = 7.1 Hz, 2H), 7.67 (d, J = 7.9 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.35 – 7.27 (m, 4H), 7.25 – 7.16 (m, 3H), 7.09 – 6.99 (m, 2H), 6.01 (s, 1H), 3.63 (s, 3H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 155.2, 143.3, 138.1, 137.4, 130.6, 129.5, 129.4, 129.1, 127.9, 124.9, 122.9, 122.3, 121.6, 120.0, 110.0, 109.8, 72.1, 30.9, 12.1, 0.9. Accurate mass for product **4** could not be detected because of rapid fragmentation (loss of (TMSO)NPh) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{23}H_{21}N_2O$ $[M–H]^+$, 341.1648; found, 341.1647.



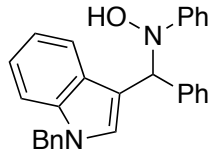
***N*-((5-Bromo-1-methyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (5)** The title compound[16] was prepared according to the General Procedure at 0 °C for 30 min reaction time, using 5-bromo-1-methyl-1*H*-indole (210 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (221 mg, 1.10 mmol). Purification by column chromatography on neutral alumina (0-1% EtOAc/hexanes doped with 1% diethylamine) provided the product as a sticky yellow solid (445 mg, 93% yield): IR (film) 3062, 3032, 2957, 2922, 1603, 1486, 1474, 1249, 888, 872, 838, 788, 755, 695 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.91 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 6.8 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.42 – 7.32 (m, 4H), 7.34 – 7.24 (m, 3H), 7.22 (d, J = 8.7 Hz, 1H), 7.03 (tt, J = 7.4, 1.3 Hz, 1H), 6.03 (s, 1H), 3.73 (s, 3H), -0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 153.1, 140.1, 135.3, 131.0, 129.9, 129.8, 128.0, 127.8, 127.2, 124.0, 122.7, 122.3, 119.5, 112.2, 111.8, 110.7, 70.2, 32.9, -1.1. Accurate mass for product **5** could not be detected because of rapid fragmentation (loss of (TMSO)NPh) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{22}H_{18}N_2OBr$ $[M–H]^+$, 405.0597, 407.0579; found, 405.0603, 407.0575.



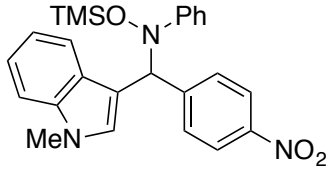
***N*-((5-methoxy-1-methyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (6)** The title compound[16] was prepared according to the General Procedure at 0 °C for 30 min reaction time, using 5-methoxy-1-methyl-1*H*-indole (161 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (221 mg, 1.10 mmol). Purification by column chromatography on neutral alumina (0-1% EtOAc/hexanes doped with 1% diethylamine) provided the product as a yellow solid (415 mg, 96% yield): mp: 43-48 °C; IR (film) 3062, 3028, 2949, 2833, 1487, 1600, 1487, 1450, 1248, 1213, 1173, 1060, 883, 837, 791, 755, 695 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.67 – 7.60 (m, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.33 (m, 1H), 7.33– 7.29 (m, 2H), 7.27 – 7.22 (m, 3H), 7.21 (d, J = 2.5 Hz, 1H), 7.13 (s, 1H), 7.01 (tt, J = 7.1, 1.2 Hz, 1H), 6.93 (dd, J = 8.8, 2.5 Hz, 1H), 6.02 (s, 1H), 3.89 (s, 3H), 3.74 (s, 3H), -0.04 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 153.9, 153.2, 140.5, 132.1, 130.5, 130.0, 128.6, 128.0, 127.8, 127.2, 122.6, 119.7, 111.8, 111.5, 109.9, 101.7, 70.6, 55.7, 32.9, -0.9; Accurate mass for product **6** could not be detected because of rapid fragmentation (loss of (TMSO)NPh) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{23}H_{21}N_2O_2$ $[M–H]^+$, 357.1598; found, 357.1590.



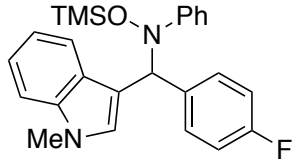
***N*-((1-Allyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (7)** The title compound[16] was prepared according to a General Procedure at 0 °C for 30 min reaction time, using *N*-allylindole (157 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (217 mg, 1.10 mmol). Purification by column chromatography on neutral alumina (hexanes doped with 1% diethylamine) provided the as a sticky yellow solid (314 mg, 74% yield): IR (film) 3060, 2957, 2904, 1596, 1486, 1466, 1451, 1334, 1248, 1179, 10104, 887, 838, 736, 695 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.75 (d, J = 7.9 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.45 – 7.30 (m, 6H), 7.30 – 7.21 (m, 4H), 7.16 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.04 – 6.96 (m, 1H), 6.14 – 5.98 (m, 2H), 5.27 – 5.22 (m, 1H), 5.11 – 4.98 (m, 1H), 4.82 – 4.70 (m, 2H), -0.06 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2) δ 153.3, 140.4, 136.0, 133.8, 130.1, 128.9, 128.5, 128.0, 127.8, 127.2, 122.7, 121.5, 119.8, 119.7, 119.1, 116.6, 112.6, 109.5, 70.6, 48.7, -0.9. HRMS (ESI, TOF): Exact mass calcd for $C_{27}H_{29}N_2OSi$ $[M–H]^+$, 425.2044; found, 425.2045.



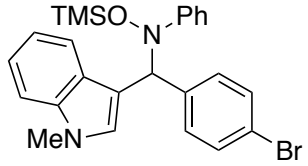
***N*-((1-Benzyl-1*H*-indol-3-yl)(phenyl)methyl)-*N*-phenylhydroxylamine (8)** The title compound[16] was prepared according to a variation of the General Procedure at –78 °C for a 1 h reaction time, using *N*-benzylindole (207 mg, 1.00 mmol) and *N*,α-diphenyl nitrone (217 mg, 1.10 mmol). The unpurified product that resulted from the General Procedure was dissolved in THF (10 mL) and cooled to –20 °C, then treated with tetrabutylammonium fluoride (1100 μL, 1.0 M in THF, 1.10 mmol). After 10 min, the reaction mixture was partitioned between saturated $NaHCO_3$ (50 mL) and Et_2O (50 mL). The layers were separated, and the organic layer was diluted with hexanes (150 mL) and dried over Na_2SO_4. The solids were removed by filtration and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel (2% EtOAc/hexanes). The product was isolated as a pale yellow solid (278 mg, 69% yield): IR (film) 3508, 3061, 3030, 2920, 2867, 1596, 1489, 1466, 1452, 1356, 1336, 1173, 740, 695 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.58 (dt, *J* = 7.5, 1.4 Hz, 2H), 7.51 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.36 (t, *J* = 8.3 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.28 – 7.19 (m, 5H), 7.17 – 7.12 (m, 2H), 7.07 – 7.00 (m, 3H), 6.94 (tt, *J* = 7.1, 1.4 Hz, 1H), 6.23 (s, 1H), 5.31 (s, 2H), 5.17 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 151.7, 140.2, 137.7, 136.4, 129.2, 128.8, 128.6, 128.5, 128.1, 127.9, 127.4, 127.2, 126.5, 121.8, 121.7, 119.9, 119.4, 117.1, 112.7, 109.8, 67.1, 50.0; HRMS (ESI, TOF): Exact mass calcd for $C_{28}H_{23}N_2O$ $[M–H]^+$, 403.1805; found, 403.1808.



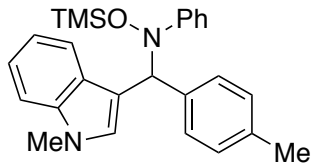
***N*-((1-Methyl-1*H*-indol-3-yl)(4-nitrophenyl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (9)** The title compound[16] was prepared according to the General Procedure at –78 °C for a 3 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*E*)-1-(4-nitrophenyl)-*N*-phenylmethanimine oxide (242 mg, 1.00 mmmol) as the nitrone. The product was isolated by column chromatography on silica gel (2-20% EtOAc/hexane) as a foamy yellow solid (368 mg, 82% yield): mp: 53-58 °C; IR (film) 3061, 2966, 2907, 1593, 1516, 1487, 1344, 1249, 892, 839, 737, 696 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.21 – 8.10 (m, 2H), 7.82 – 7.71 (m, 2H), 7.60 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.32 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.28 – 7.15 (m, 5H), 7.13 (s, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.00 – 6.90 (m, 1H), 6.03 (s, 1H), 3.77 (s, 3H), -0.19 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 152.7, 148.1, 147.0, 136.7, 130.7, 129.8, 128.1, 127.8, 123.2, 122.9, 121.6, 119.8, 119.3, 119.2, 110.8, 109.3, 70.1, 32.8, -1.0; HRMS (ESI, TOF): Exact mass calcd for $C_{25}H_{27}N_3O_3SiNa$ $[M+Na]^+$, 468.1714; found, 468.1721.



***N*-((4-Fluorophenyl)(1-methyl-1*H*-indol-3-yl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (10)** The title compound[16] was prepared according to the General Procedure at –78 °C for a 3 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*E*)-1-(4-fluorophenyl)-*N*-phenylmethanimine oxide (215 mg, 1.00 mmol) as the nitrone. The product was isolated by column chromatography on silica gel (0-2% EtOAc/hexane) as a foamy tan solid (289 mg, 69% yield): mp: 36-39 °C; IR (film) 3058, 2956, 2904, 1596, 1506, 1249, 1220, 1153, 891, 838, 736, 695 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.65 – 7.50 (m, 3H), 7.31 (dt, J = 8.2, 0.9 Hz, 1H), 7.27 – 7.14 (m, 6H), 7.11 – 6.98 (m, 3H), 6.94 (ddt, J = 7.3, 6.5, 1.5 Hz, 1H), 5.97 (s, 1H), 3.77 (s, 3H), -0.15 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 162.0 (d, J = 244.5 Hz), 153.0, 136.6, 136.4 (d, J = 3.0 Hz), 131.7 (d, J = 7.9 Hz), 129.6, 128.0 (double intensity), 122.6, 121.4, 119.4 (double intensity), 118.9, 114.4 (d, J = 21.1 Hz), 111.8, 109.1, 69.6, 32.7, -1.1; HRMS (ESI, TOF): Exact mass calcd for $C_{25}H_{27}FN_2OSiNa$ $[M+Na]^+$, 441.1769; found, 441.1774.

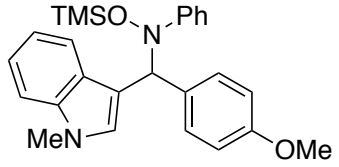


***N*-((4-Bromophenyl)(1-methyl-1*H*-indol-3-yl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (11)** The title compound[16] was prepared according to the General Procedure at –78 °C for a 3 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*E*)-1-(4-bromophenyl)-*N*-phenylmethanimine oxide (274 mg, 1.00 mmol) as the nitrone. The product was isolated by column chromatography on silica gel (0-2% EtOAc/hexane) as a foamy yellow solid (337 mg, 70% yield): mp: 39-44 °C; IR (film) 3058, 3027, 2955, 2904, 1593, 1486, 1326, 1249, 1011, 890, 837, 736, 695 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.65 (dt, J = 7.9, 1.0 Hz, 1H), 7.49 (s, 4H), 7.33 (dt, J = 8.3, 0.9 Hz, 1H), 7.29 – 7.19 (m, 5H), 7.14 (s, 1H), 7.10 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 6.99 – 6.92 (m, 1H), 5.97 (s, 1H), 3.77 (s, 3H), -0.12 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 153.0, 139.6, 136.7, 131.8, 130.8, 129.7, 128.03, 128.00, 122.8, 121.4, 120.9, 119.6, 119.5, 118.9, 111.6, 109.1, 69.9, 32.7, -1.1; HRMS (ESI, TOF): Exact mass calcd for $C_{25}H_{27}BrN_2OSiNa$ $[M+Na]^+$, 501.0968; found, 501.0975.

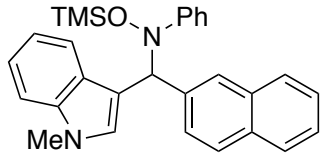


***N*-((1-Methyl-1*H*-indol-3-yl)(*p*-tolyl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (12)** The title compound[16] was prepared according to a

variation of the General Procedure at –78 °C for a 3 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*E*)-*N*-phenyl-1-(*p*-tolyl)methanimine oxide (211 mg, 1.00 mmol) as the nitrone. Unlike the General Procedure, column chromatography of the product was not performed. The product was recovered as a pale yellow oil (391 mg, 94% yield): IR (film) 3713, 2961, 2871, 1599, 1485, 1248, 1058, 1013, 383, 736, 695 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.64 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.31 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.27 – 7.11 (m, 8H), 7.07 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.96 – 6.87 (m, 1H), 5.98 (s, 1H), 3.76 (s, 3H), 2.36 (s, 3H), -0.16 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 153.2, 137.4, 136.8, 136.6, 129.9, 129.7, 128.4, 128.2, 128.0, 122.4, 121.3, 119.6, 119.4, 118.8, 112.4, 109.1, 70.0, 32.7, 20.8, -1.0; HRMS (ESI, TOF): Exact mass calcd for $C_{26}H_{30}N_2OSiNa$ $[M+Na]^+$, 437.2020; found, 437.2032.

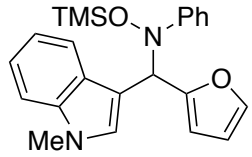


***N*-((4-Methoxyphenyl)(1-methyl-1*H*-indol-3-yl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (13)** The title compound[16] was prepared according to a variation of the General Procedure at 0 °C for a 30 min reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine oxide (251 mg, 1.10 mmol) as the nitrone. Purification by column chromatography on neutral alumina (hexanes doped with 1% diethylamine) provided the product as a sticky yellow foam (316 mg, 74% yield): IR (film) 3062, 2959, 2908, 2832, 1596, 1510, 1485, 1246, 1176, 1033, 891, 836, 799, 737 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.67 (d, *J* = 8.1 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.38 – 7.15 (m, 7H), 7.10 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.01 – 6.92 (m, 1H), 6.92 – 6.83 (m, 2H), 6.00 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), -0.11 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 160.8, 155.1, 138.5, 134.4, 133.0, 131.4, 130.1, 129.8, 124.3, 123.2, 121.5, 121.3, 120.7, 114.9, 114.4, 110.9, 71.7, 57.0, 34.5, 0.9. Accurate mass for product **13** could not be detected because of rapid fragmentation (loss of (TMSO)NPh) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{23}H_{21}N_2O_2$ $[M–H]^+$, 357.1598; found, 357.1600.

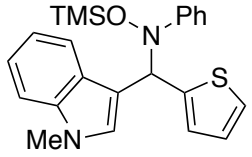


***N*-((1-Methyl-1*H*-indol-3-yl)(naphthalen-2-yl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (14)** The title compound[16] was prepared according to a variation of the General Procedure at –78 °C for a 3 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*E*)-1-(naphthalen-2-yl)-*N*-phenylmethanimine oxide (247 mg, 1.00 mmol) as the nitrone. Unlike the General Procedure, column

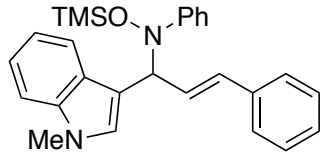
chromatography of the product was not performed. The product was recovered as a pale yellow solid (422 mg, 94% yield): mp: 60-62 °C; IR (film) 3056, 2956, 1594, 1486, 1331, 1248, 914, 881, 839, 737, 695 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.01 – 7.93 (m, 1H), 7.93 – 7.80 (m, 4H), 7.68 – 7.64 (m, 1H), 7.55 – 7.47 (m, 2H), 7.39 – 7.29 (m, 3H), 7.29 – 7.17 (m, 4H), 7.12 – 6.89 (m, 2H), 6.21 (s, 1H), 3.79 (s, 3H), -0.14 - -0.16 (m, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 153.2, 138.3, 136.6, 133.2, 132.7, 129.9, 128.5, 128.4, 128.3, 128.02, 127.96, 127.4, 127.2, 125.8, 125.7, 122.6, 121.4, 119.5 (double intensity), 118.9, 111.8, 109.1, 70.4, 32.7, -0.9; HRMS (ESI, TOF): Exact mass calcd for $C_{29}H_{30}N_2OSiNa$ $[M+Na]^+$, 473.2020; found, 473.2026.



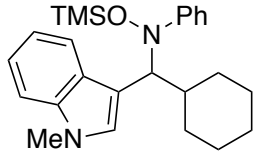
***N*-(Furan-2-yl(1-methyl-1*H*-indol-3-yl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (15)** UNLIKE THE GENERAL PROCEDURE, THIS REACTION WAS PERFORMED ON A 0.75 MMOL SCALE. The title compound[16] was prepared according to a variation of the General Procedure. To an oven-dried round-bottomed flask under N_2 atmosphere were added (*E*)-1-(furan-2-yl)-*N*-phenylmethanimine oxide (155 mg, 0.83 mmol), tetrahydrofuran (THF, 8.0 mL), *N*-methylindole (94 μL, 98 mg, 0.75 mmol), and *i*-Pr_2NEt (171 μL, 127 mg, 0.98 mmol). The mixture was cooled to 0 °C appropriate reaction temperature, and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 163 μL, 200 mg, 0.90 mmol) was added dropwise. The mixture was stirred for the 30 min, then treated with pyridine (158 μL, 154 mg, 1.95 mmol). The mixture was quickly passed through a column of silica (4 cm x 1 cm) with Et_2O (20 mL). The solvent was removed in vacuo, and the residue was treated with additional pyridine (158 μL, 154 mg, 1.95 mmol) and purified by column chromatography on neutral alumina (0-1% EtOAc/hexanes doped with 1% diethylamine) to provide the product as a sticky yellow-orange foam (277 mg, 94% yield): IR (film) 3713, 2957, 2863, 1685, 1603, 1488, 1248, 1011, 883, 840, 734, 694 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.67 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.45 (dd, *J* = 0.9, 1.9 Hz, 1H), 7.32 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.20 – 7.18 (m, 1H), 7.18 – 7.13 (m, 4H), 7.10 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.00 – 6.94 (m, 1H), 6.36 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.28 (d, *J* = 3.2 Hz, 1H), 5.94 (s, 1H), 3.77 (s, 3H), -0.09 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 153.6, 152.6, 141.4, 136.5, 129.9, 128.0, 127.9, 123.0, 121.3, 119.9, 119.6, 118.9, 110.2, 110.0, 109.6, 109.1, 64.3, 32.7, -1.2; HRMS (ESI, TOF): Exact mass calcd for $C_{23}H_{26}N_2O_2SiNa$ $[M+Na]^+$, 413.1656; found, 413.1659.



***N*-((1-Methyl-1*H*-indol-3-yl)(thiophen-2-yl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (16)** The title compound[16] was prepared according to a variation of the General Procedure at 0 °C for a 3 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (*E*)-*N*-phenyl-1-(thiophen-2-yl)methanimine oxide (203 mg, 1.00 mmol) as the nitrone. Unlike the General Procedure, column chromatography of the product was performed using basic alumina. The product was recovered as an orange foam (312 mg, 77% yield): IR (film) 2953, 2894, 1593, 1485, 1377, 1249, 1200, 1010, 886, 841, 738, 698 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.27 – 7.19 (m, 5H), 7.15 (t, *J* = 8.1 Hz, 1H), 7.05 (s, 1H), 7.00 – 6.95 (m, 2H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.26 (s, 1H), 3.76 (s, 3H), -0.18 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 152.6, 141.6, 136.7, 129.8, 128.0, 127.8, 126.9, 125.6, 125.2, 122.8, 121.5, 119.5, 119.4, 119.0, 113.3, 109.2, 66.3, 32.7, -1.2; HRMS (ESI, TOF) showed no mass corresponding to this compound. A mass that corresponds to the cation formed by loss of the silyloxyamino group was observed, however: Exact mass calcd for $C_{14}H_{12}NS$ $[M–C_9H_{14}NOSi]^+$, 226.0688; found, 226.0685.



(*E*)-*N*-(1-(1-Methyl-1*H*-indol-3-yl)-3-phenylallyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (17) The title compound[16] was prepared according to a variation of the General Procedure at 0 °C for a 0.5 h reaction time, using *N*-methylindole (125 μL, 131 mg, 1.00 mmol) and (1*E*,2*E*)-*N*,3-diphenylprop-2-en-1-imine oxide (223 mg, 1.00 mmol) as the nitrone. The product was purified by column chromatography on basic alumina (0-2% EtOAc/hexane) and recovered as a yellow foam (267 mg, 63% yield): IR (film) 3026, 2956, 1596, 1485, 1328, 1248, 1202, 887, 839, 737, 693 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.78 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.27 – 7.18 (m, 6H), 7.12 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.03 (s, 1H), 7.02 – 6.94 (m, 1H), 6.88 (dd, *J* = 16.0, 8.1 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), -0.06 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 152.9, 137.2, 136.9, 131.8, 128.7, 128.5 (double intensity), 127.9, 127.8, 127.3, 126.3, 123.0, 121.3, 120.3, 120.0, 118.9, 112.9, 109.2, 69.3, 32.6, -0.8; HRMS (ESI, TOF) showed no mass corresponding to this compound. A mass that corresponds to the cation formed by loss of the silyloxyamino group was observed, however: Exact mass calcd for $C_{18}H_{16}N$ $[M–C_9H_{14}NOSi]^+$, 246.1277; found, 246.1280.



***N*-(Cyclohexyl(1-methyl-1*H*-indol-3-yl)methyl)-*N*-phenyl-*O*-(trimethylsilyl)hydroxylamine (18)** The title compound[16] was prepared according to a variation of the General Procedure at 0 °C for a 3 h reaction time, using *N*-methylindole

(125 μL, 131 mg, 1.00 mmol) and (*Z*)-1-cyclohexyl-*N*-phenylmethanimine oxide (203 mg, 1.00 mmol) as the nitrone. Purification by column chromatography on silica gel (1-2% EtOAc/hexanes doped with 1% diethylamine) provided the product as a white powder (347 mg, 85% yield): mp: 115 – 116 °C; IR (film) 2956, 2916, 2846, 1593, 1482, 1448, 1328, 1248, 1008, 971, 927, 918, 901, 874, 834, 773, 7760, 731, 699 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.38 (bd, *J* = 7.8 Hz, 1H), 7.25 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.19 – 7.07 (m, 3H), 7.02 – 6.93 (m, 3H), 6.91 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.70 (s, 1H), 4.19 (d, *J* = 10.5 Hz, 1H), 3.69 (s, 3H), 2.74 (d, *J* = 13.1 Hz, 1H), 2.18 (q, *J* = 11.2 Hz, 1H), 2.00 – 1.83 (m, 1H), 1.81 – 1.67 (m, 1H), 1.66 – 1.57 (m, 1H), 1.52 – 1.34 (m, 2H), 1.34 – 1.15 (m, 3H), 0.82 – 0.72 (m, 1H), 0.17 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 154.3, 136.3, 129.3, 129.1, 127.7, 122.1, 120.6, 119.5, 118.4, 109.8, 108.8, 74.0, 39.8, 32.7, 32.5, 30.9, 26.8, 26.4, 26.1, -0.4. Accurate mass for product **18** could not be detected because of rapid fragmentation (loss of (TMSO)NPh) during mass spectrometry. Accordingly, a small portion of the product was deprotected (1.1 equiv TBAF, THF, –20 °C, 1h) and the free hydroxylamine was analyzed: HRMS (ESI, TOF): Exact mass calcd for $C_{22}H_{25}N_2O$ $[M–H]^+$, 333.1961; found, 333.1946.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

Supplementary data (^1H and ^{13}C NMR spectra for compounds **3a-18** and table of comparison of promoting agents) associated with this article can be found, in the online version, at XXX.

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[1] For an overview of the synthesis of biologically active α-(1*H*-indol-3-yl)benzylamines, see: (a) *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, 2010. (b) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley-VCH: Chichester, 2009. (c) D. J. Faulkner, *Nat. Prod. Rep.*, **2002**, *19*, 1–48. (d) Barton, D. H. R.; Nakanishi, K.; Meth-Cohn, O.; Kelly, J. W. *Comprehensive Natural Products Chemistry*; Pergamon: Oxford, 1999.

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[3] For representative examples, see: (a) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. The highly enantioselective addition of indoles to N-acyl imines with use of a chiral phosphoric acid catalyst. *Org. Lett.* **2007**, *9*, 2609-2611. (b) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, Li. Asymmetric Friedel-crafts reaction of indoles with imines by an organic catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 8156-8157. (c) Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. Squaramide-catalyzed enantioselective Friedel-Crafts reaction of indoles with imines. *Chem. Commun.* **2010**, *46*, 3004-3006. (d) Montesinos-Magraner, M.; Vila, C.; Rendon-Patino, A.; Blay, G.; Fernandez, I.; Munoz, M. C.; Pedro, J. R. Organocatalytic Enantioselective Friedel–Crafts Aminoalkylation of Indoles in the Carbocyclic Ring. *ACS Catal.* **2016**, *6*, 2689-2693. (e) Lee, S. G.; Kim, S.-G. An asymmetric Brønsted acid-catalyzed Friedel–Crafts reaction of indoles with cyclic *N*-sulfimines. *RSC Adv.* **2017**, *7*, 34283-34286. (f) Vila, C.; Tortosa, A.; Blay, G.; Munoz, M. C.; Pedro, J. R. Organocatalytic enantioselective functionalization of indoles in the carbocyclic ring with cyclic imines. *New J. Chem.* **2019**, *43*, 130-134.

[4] (a) Chalaye-Mauger, H.; Denis, J.-N.; Averbuch-Pouchot, M.-T.; Vallée, Y. The reactions of nitrones with indoles. *Tetrahedron* **2000**, *56*, 791-804. (b) Denis. J.-N.; Mauger, H.; Vallée, Y. The reaction of nitrones with indoles. Synthesis of asymmetrical diindolylalcanes. *Tetrahedron Lett.* **1997**, *38*, 8515-8518.

[5] For examples, see: (a) Banerji, A.; Mukhopadhyay, A. K. Reactions of some indole derivatives with nitrones *Indian J. Chem., Sect. B* **1982**, *21B*, 239-241. (b) Zheng, L.; Gao, F.; Yang, C.; Gao, G.-L.; Zhao, Y.; Gao, Y.; Xia, W. Visible-light-mediated anti-regioselective nitrone 1,3-dipolar cycloaddition reaction and synthesis of bisindolylmethanes *Org. Lett.* **2017**, *19*, 5086-5089.

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[11] See supporting information (Table S1) for an illustration of the results for various promoters.

[12] Despite our adherence to this precaution, limited preliminary results suggest that this step may be unnecessary. A control experiment wherein the pyridine quench was omitted revealed no evidence of the formation of the undesired 2:1 adduct during workup.

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