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Direct synthesis of 3-arylindoles via annulation of aryl hydroxylamines with alkynes

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ABSTRACT

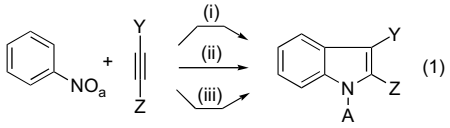
3-Arylindoles are produced in moderate to excellent yields from the reaction between aryl hydroxylamines and alkynes catalyzed by 10 mol % iron(II) phthalocyanine [Fe(Pc)]. Terminal and internal alkynes afford 3-aryl substituted indoles exclusively. Electron-donating and -withdrawing groups are tolerated on the aryl hydroxylamine. A few bioactive indoles are synthesized as well as several new indoles using this one-step intermolecular annulation procedure.

1. Introduction

Indoles are an important class of *N*-heterocycles due to their frequent occurrence as natural products and bioactive compounds. Many methods have been developed for their preparation,[1] yet new and improved approaches are still being sought which, employ more accessible starting materials, milder reaction conditions, are functional group-tolerant, and achieve improved regioselectivity. Especially attractive, but relatively rare, are methods, which produce indoles by annulation of *N*-aromatic precursors, as in the Fischer-indole synthesis.[2,3] The search for a general and efficient annulation method has spawned several transition metal-promoted routes to indoles,[4] though most of these are cyclizations requiring a prefunctionalized *ortho*-substituted *N*-aromatic substrate.[5]

Our interest in metal-promoted nitrogenation reactions of hydrocarbons[6] led to the recent discoveries of indole-forming reactions of alkynes with nitro-[7] and nitroso[8]-aromatics (Eq. 1). The indole skeleton in each of these reactions is formed via a novel cyclocondensation of a nitrosoarene with the alkyne.[9] The intervening *N*-hydroxyindole can either be trapped as the *N*-methoxy indole[8b] or reduced in situ in a second step to the indole (Scheme 1).[7,8a]

In order to develop an efficient one step method to form the parent (NH) indoles that did not require the use of high pressures of CO and to broaden the scope of the *N*-aromatic precursors, aryl hydroxylamines[10] were considered attractive candidates. Since redox metal-catalyzed allylic aminations of olefins with aryl hydroxylamines[6,11] involve in situ hydroxylamine oxidation, ene reaction of the resulting nitrosoarene,[12] and reduction of the allyl hydroxylamine, we envisioned a similar catalytic pathway for alkyne indolization by aryl hydroxylamines via nitrosoarene and *N*-hydroxyindole intermediates.



(1)

Scheme 1. (i) a=2, CO/[CpRu(CO)$_2$]$_2$, A=H; (ii) a=1, Δ, A=OH; (iii) a=1, Δ/Me$_2$SO$_4$, A=OMe.

2. Results and discussion

Utilizing the conditions reported for the *N*-hydroxyindole preparation,[8a] a survey and initial optimization study (Table 1) were conducted on the reaction of PhNHOH with excess phenyl acetylene in the presence of various redox-active complexes, including (dtc)$_2$MoO$_2$, (dipic)MoO$_2$(HMPA), FeCl$_2$/FeCl$_3$, Cu(CH$_3$CN)$_4$PF$_6$, CuCl$_2$·2H$_2$O, and Fe(Pc)[6,11] (dtc=*N*,*N*-diethyl dithiocarbamate, dipic=2,6-pyridinedicarboxylate, HMPA=hexamethyl phosphortriamide, Pc=phthalocyanine), and solvents (benzene, dioxane, toluene, 1,2-dichloroethane, EtOH, CH$_3$CN, *i*-PrOH, *t*-BuOH, and chlorobenzene). GC, GC–MS, and TLC analysis indicated the production of 3-phenylindole with several of these systems (Table 1) with the best

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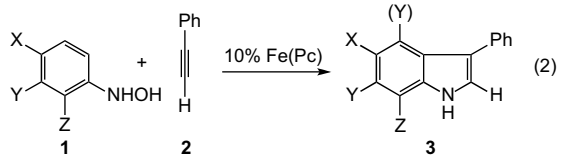
Table 1
Transition metal-catalyzed indolization of phenyl acetylene and *N*-phenylhydroxylamine[a]

Entry	Solvent	Catalyst[b]	Yield[c] (%)
1	Benzene	$Mo(dtc)_2O_2$	51
2	Benzene	$(dipic)MoO_2(HMPA)$	11
3	Benzene	9:1 $FeCl_2/FeCl_3$	34[d]
4	Benzene	$Cu(CH_3CN)_4PF_6$	15
5	Benzene	$CuCl_2 \cdot H_2O$	19
6	Benzene	Fe(Pc)	66
7	Dioxane	Fe(Pc)	70
8	Toluene	Fe(Pc)	84
9	Toluene	Fe(Pc)	70[e]

[a] Phenylhydroxylamine (0.5 mmol) added by syringe pump (7–8 h), 10 mmol phenyl acetylene, Ar, reflux.
[b] Cat. (10 mol %).
[c] GC yield using naphthalene as internal standard.
[d] Anhydrous Fe salts or FeX_n hydrates.
[e] Fe(Pc) (5 mol %).

results being obtained with commercially available and inexpensive Fe(Pc) as catalyst. Minor products include azoxybenzene (3–10%), azobenzene (0–2%), and aniline (0–15%). By slowly adding PhNHOH (0.5 mmol in toluene, 7–8 h) to a refluxing solution of phenyl acetylene (10 mmol) and Fe(Pc) (0.05 mmol) an 84% yield of 3-phenylindole (GC) was achieved.

Using the optimized conditions, a series of substituted *N*-aryl hydroxylamines were tested with phenyl acetylene in the indolization reaction (Scheme 2, Table 2). Both electron-donating and -withdrawing groups are tolerated on the aryl hydroxylamine. In terms of regioselectivity of the alkyne cycloaddition, 3-aryl isomers are solely detected in all examples. From *meta*-substituted *N*-aryl hydroxylamine substrates (entries 6–8), mixtures of 4- and 6-substituted indoles were obtained, with the 4-substituted indole slightly favored in each case. 3-Phenyl-benz[*g*]indole (entry 9) was also produced regioselectively from the annulation of alkyne with 1-hydroxylamino-naphthalene. Yields of indoles from the current one-step procedure are comparable (3–15% lower) to those produced by the two-step *N*-hydroxyindole preparation and its reduction (H_2/10% Pd/C) to the free indole.[8b]



Scheme 2.

Representative terminal and internal aryl alkynes were effective partners with good to excellent yields produced from terminal alkynes (Table 2, entry 1) and a moderate yield from 3-phenylpropyne (Table 3, entry 10). The 2-Me-3-Ph-indole is isolated exclusively, further demonstrating the 3-aryl regioselectivity of the reaction. An exploration of the alkyne substrate scope is summarized in Table 3. A scale-up reaction using 2.0 mmol of PhNHOH and 10 equiv of 3,4-dimethoxyphenyl acetylene resulted in a nearly identical yield (55%, entry 12), with ~98% of the unreacted alkyne recovered. The attempt to utilize cyclooctyne as a substrate in order to generate a precursor to the anti-depressant iprindole[13] resulted in cyclotrimerization[14] in the presence of Fe(Pc) in either refluxing toluene or benzene, with no indole formed. Owing to the technical ease of isolation of the parent (NH) indoles using the present one-step procedure, several previously unused *N*-aromatic substrates and/or alkynes were utilized in this study resulting in new indoles **3f**, **3f′**, **3h**, **3h′**, **3i**, **3l**, and **3m**. Of particular interest are indoles **3l** and **3m**, which both possess interesting bioactivity[15] and relatively limited synthetic approaches.[16] It is noteworthy that indole **3m** is produced in 72% yield despite having a potentially *N*-coordinating alkyne used in large excess relative to the catalyst.

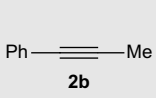
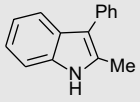
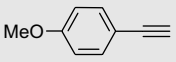
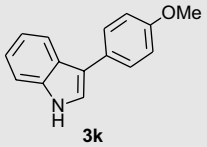
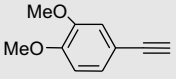
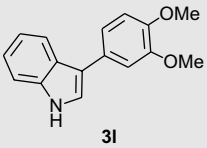
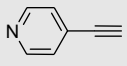
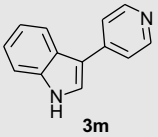
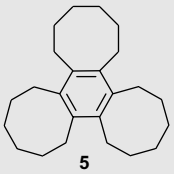
To address the issue of whether the free nitrosoarene is generated in the Fe(Pc)-catalyzed reactions, the trapping experiment shown in Scheme 3 was conducted. When the PhNHOH/PhC≡CH reaction was carried out in the presence of 2,3-dimethyl-1,3-butadiene (10 equiv of diene, 10 equiv of alkyne), none of the indole was detected, but rather the hetero Diels–Alder product[17] was formed and verified by ^{1}H NMR and GC–MS. This result strongly suggests the intermediacy of PhNO in the Fe(Pc)-catalyzed reaction.

Table 2
Fe(Pc)-catalyzed preparation of indoles from phenyl acetylene and *N*-aryl hydroxylamines[a] (Scheme 2)

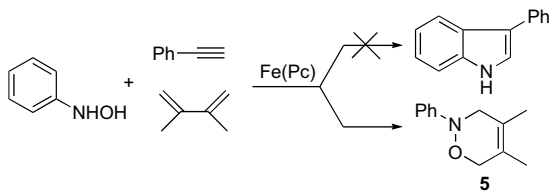
Entry	1	X	Y	Z	3	% Isolated yield
1	**1a**	H	H	H	**3a**	81
2	**1b**	Me	H	H	**3b**	55
3[b]	**1c**	CN	H	H	**3c**	55
4	**1d**	Cl	H	H	**3d**	38
5	**1e**	H	H	Me	**3e**	45
6	**1f**	H	Me	H	**3f**, **f′**	47 (4-Me/6-Me=27:20)
7	**1g**	H	CF_3	H	**3g**, **g′**	65 (4-CF_3/6-CF_3=34:31)
8	**1h**	Cl	Cl	H	**3h**, **h′**	55 (4,5-Cl/5,6-Cl=34:21)
9	**1i**	H	$-C_4H_4-$		**3i**	37

[a] Fe(Pc) (10 mol %), refluxing toluene, 7–8 h addition of aryl hydroxylamine (procedure in Experimental section).
[b] Dioxane used as solvent.

Table 3
Fe(Pc)-catalyzed preparation[a] of indoles from aryl alkynes and **1a** (*N*-phenylhydroxylamine) (Scheme 2)

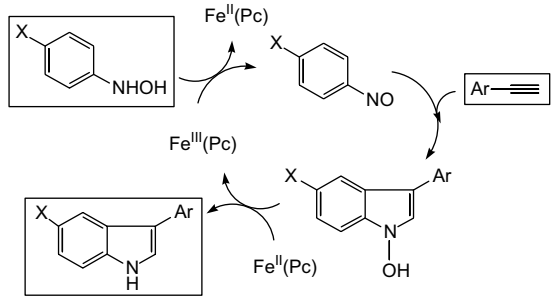
Entry	Alkyne	Major product	% Isolated yield
10	 **2b**	 **3j**	25
11	 **2c**	 **3k**	88
12	 **2d**	 **3l**	57 (55)[b]
13[c]	 **2e**	 **3m**	72
14[d]	 **4**	 **5**	>50

[a] Fe(Pc) (10 mol %), refluxing toluene, 7–8 h addition of **1a**.
[b] Scale-up reaction: 10 equiv alkyne, 32 h addition of **1a**.
[c] Alkyne (17 equiv), reaction run in dark.
[d] No indole detected.



Scheme 3.

The catalytic reaction pathway is thus suggested to proceed via PhNHOH oxidation by a Fe^{III}(Pc) species[18] to PhNO, nitroso/alkyne cyclocondensation to the *N*-hydroxyindole, and reduction of the latter to the indole by Fe^{II}(Pc) (Scheme 4).



Scheme 4.

3. Conclusions

In summary, we have developed a new metal-catalyzed procedure to produce 3-arylindoles in moderate to excellent yields. Electron-donating and -withdrawing *N*-aryl hydroxylamines are both suitable substrates, as well as a variety of aryl alkynes, including one with *N*-coordinating ability. Terminal and internal alkynes can be applied with exceptional regioselectivity to 3-aryl products. Advantages of the system include the production of the parent (NH) indole in a one-step, one-pot reaction that doesn't require high pressures of CO, and the use of inexpensive and commercially available Fe(Pc) as catalyst. The *N*-aryl hydroxylamines used are conveniently prepared in one step via reduction of nitroaromatics, and purified by recrystallization. In contrast, the nitrosoaromatics utilized in our previous method are formed in one step via oxidation of amines with purification generally by column chromatography. In this intermolecular annulation, the system does not require a *ortho*-substituted or activated *N*-aromatic substrates scaffold, resulting in a highly convergent indole synthesis. Efforts to further demonstrate the synthetic utility of this new direct indolization reaction are currently underway.

4. Experimental

4.1. General

Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, or GFS. Nitroaromatics used in reduction to *N*-aryl hydroxylamines were used without any purification. *N*-Aryl hydroxylamines **1a**,[10] **1e**,[10] **1f**,[10] **1g**,[19a] **1h**,[19b] and **1i**[19c] were prepared using literature procedure (Ref. 10b), compounds **1b**,[10] **1c**,[19d] and **1d**[10] were prepared by literature procedure (Ref. 10d), and each compound was determined to be pure by comparison to individual known data. All *N*-aryl hydroxylamines were stored under argon and kept below 0 °C. Purchased alkynes were purified by distillation before use, and alkynes **2b**,[20] **2d**,[21] **2e**,[22] and **4**[23] were all prepared according to their literature procedures, and each compound exhibited appropriate ^{1}H and/or ^{13}C NMR data. Cyclooctyne trimer **5** exhibited appropriate ^{1}H and ^{13}C NMR data as reported.[14b] Toluene, benzene, and dioxane were distilled prior to use over Na/benzophenone. All other solvents including those used in chromatography were used without any purification. Visualization of the developed chromatogram was performed under UV light or I_2 stain. ^{1}H NMR spectra were obtained at 300 MHz and ^{13}C NMR spectra at 60 MHz; NMR spectra were internally referenced to residual protio solvent signals. Data for ^{1}H NMR data are reported as follows: chemical shift (δ ppm), multiplicity (br=broad, s=singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets), coupling constant (Hz), integration, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Mass spectra were acquired in methanol or acetonitrile solution by ESI. Naphthalene was used as an internal standard for GC yield determinations.

4.2. General procedure for the preparation of 3-arylindoles (3)

A mixture of 0.05 mmol of Fe(Pc), 10 mmol of alkyne, and 15 mL of toluene was stirred at reflux under argon and to this was added 0.50 mmol of the *N*-aryl hydroxylamine in 5–6 mL of toluene by syringe pump (7–8 h). After the addition was complete, reflux was continued overnight (8–12 h). After cooling, the mixture was evaporated to a solid under vacuum. Flash chromatography of the residue over silica gel (20% EtOAc/hexane eluant) afforded the indole products, typically as solids. All new compounds were spectroscopically pure (>95%) and exhibited appropriate ^{1}H and ^{13}C NMR spectra and MS data (provided in Supplementary data). Previously characterized indoles **3a**,[8a] **3b**,[7b,15d] **3d**,[8a] **3e**,[24] **3g**,[8a] **3g′**,[8a] **3j**,[8a] and **3k**[25] displayed ^{1}H NMR spectra and MS data that matched those reported in the respective literature (available in Supplementary data).

*4.2.1. 5-Cyano-3-phenylindole (**3c**)*

Prepared according to the general procedure from 4-cyano-*N*-phenylhydroxylamine (72 mg, 0.5 mmol) dissolved in 6 mL dioxane, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and dioxane (15 mL) to provide the title compound (60.1 mg, 0.276 mmol) in 55% yield: ^{1}H and ESI/MS data for **3c** matched those reported in the literature.[8a]

*4.2.2. 4-Methyl-3-phenylindole (**3f**) and 6-methyl-3-phenylindole (**3f′**)*

Prepared according to the general procedure from 3-methyl-*N*-phenylhydroxylamine (61.5 mg, 0.5 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide **3f** as an oily tan solid (28 mg, 0.135 mmol) in 27% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (br s, 1H, NH), 7.84 (d, J=11.4 Hz, 1H), 7.68 (dd, J=8.1 and 0.9 Hz, 2H), 7.45 (t, J=6.6 Hz, 2H), 7.29 (m, 3H), 7.05 (dd, J=8.4 and 1.2 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 137.3, 135.9, 132.5, 128.9, 127.6, 126.1, 123.8, 122.3, 121.3, 119.7, 118.4, 111.5, 21.9; HRMS (ESI) calculated for $C_{15}NH_{13}$ ($M+H^+$) requires m/z 208.1126, found m/z 208.1186.

Compound **3f′** was obtained as an orange solid (21 mg, 0.101 mmol) in 20% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (br s, 1H, NH), 7.47–7.23 (m, 6H), 7.14 (t, J=4.8 Hz, 2H), 6.89 (dd, J=6.9 and 0.9 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 137.2, 136.4, 131.5, 130.9, 127.8, 126.6, 125.4, 123.1, 122.6, 121.8, 119.9, 109.2, 21.0; LRMS (EI) m/z 207.

*4.2.3. 4,5-Dichloro-3-phenylindole (**3h**) and 5,6-dichloro-3-phenylindole (**3h′**)*

Prepared according to the general procedure from 3,4-dichloro-*N*-phenylhydroxylamine (89 mg, 0.5 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide the title compound as a beige solid (44.3 mg, 0.169 mmol) in 34% yield: ^{1}H NMR ($CDCl_3$,

300 MHz) δ 8.23 (br s, 1H, NH), 7.40 (dd, J=7.8 and 1.8 Hz, 2H), 7.34–7.27 (m, 3H), 7.23–7.16 (m, 2H), 7.11 (d, J=2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 135.6, 134.8, 131.2, 127.6, 126.9, 125.6, 124.9, 124.7, 124.6, 124.1, 119.7, 110.9; HRMS (ESI) calculated for $C_{14}NCl_2H_9$ ($M+Na^+$) requires m/z 284.0010, found m/z 284.0034, mp=90 °C.

Compound **3h′** was isolated as a white solid (28 mg, 0.107 mmol) in 21% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26 (br s, 1H, NH), 7.99 (s, 1H), 7.61 (dd, J=8.3 and 1.2 Hz, 2H), 7.55 (s, 1H), 7.47 (t, J=7.2 Hz, 2H), 7.40 (d, J=2.7 Hz, 1H), 7.33 (t, J=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 135.5, 134.5, 129.2, 127.6, 126.8, 126.5, 125.8, 124.7, 123.6, 121.1, 118.5, 113.0; LRMS (EI) m/z 261, 263.

4.2.4. 3-Phenyl-benz[g]indole (**3i**)

Prepared according to the general procedure from *N*-1-naphthyl-hydroxylamine (79.5 mg, 0.5 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide the title compound as a gray solid (45 mg, 0.185 mmol) in 37% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.97 (br s, 1H, NH), 8.06–7.96 (m, 3H), 7.74 (d, J=8.4 Hz, 2H), 7.60–7.44 (m, 6H), 7.34 (t, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 135.5, 131.3, 130.5, 128.9, 128.8, 127.8, 126.2, 125.6, 124.2, 121.8, 121.6, 121.2, 120.3, 119.8, 119.6, 119.3; HRMS (ESI) calculated for $C_{18}NH_{13}$ ($M+Na^+$) requires m/z 266.0946, found m/z 266.0996, mp=236 °C.

4.2.5. 3-(3,4-Dimethoxyphenyl)indole (**3l**)

Prepared according to the general procedure from *N*-phenylhydroxylamine (30 mg, 0.27 mmol) dissolved in 5 mL toluene, Fe(Pc) (17 mg, 0.03 mmol), 3,4-dimethoxyphenylacetylene (0.972 g, 6 mmol), and toluene (10 mL) to provide the title compound as a yellow solid (38.6 mg, 0.153 mmol) in 57% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (br s, 1H, NH), 7.92 (d, J=7.8 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.34 (d, J=2.4 Hz, 1H), 7.30–7.18 (m, 4H), 6.99 (d, J=8.1 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 149.3, 147.7, 136.8, 128.6, 126.1, 122.6, 121.5, 120.4, 119.9, 119.8, 118.4, 111.8, 111.6, 111.3, 56.2, 56.1; HRMS (ESI) calculated for $C_{16}O_2NH_{15}$ ($M+Na^+$) requires m/z 276.1000, found m/z 276.0898, mp=150–154 °C.

4.2.6. Scale-up reaction of indole (**3l**)

Prepared by four sequential 7–8 h additions (~30 h total) of *N*-phenylhydroxylamine (four portions of 50 mg, 0.45 mmol, 200 mg, and 1.8 mmol total) dissolved in 6 mL of toluene each, Fe(Pc) (113 mg, 0.2 mmol), 3,4-dimethoxyphenylacetylene (3.24 g, 20 mmol), and toluene (35 mL) followed by an additional 8 h reflux to provide the title compound as a yellow solid (249 mg, 0.984 mmol) in 55% yield. Unreacted alkyne (3.09 g, 19.0 mmol) was recovered from column chromatography isolation.

4.2.7. 3-(4-Pyridyl)indole (**3m**)

Prepared according to the general procedure for **3** (with protection from light during reaction) from *N*-phenylhydroxylamine (33 mg, 0.3 mmol) dissolved in 5 mL toluene, Fe(Pc) (17 mg, 0.03 mmol), 4-ethynylpyridine (525 mg, 5.1 mmol), and toluene (10 mL) to provide the title compound as a greenish-white solid (41.8 mg, 0.215 mmol) in 72% yield (isolated from preparatory TLC using EtOAc): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (br s, 1H, NH), 8.64 (d, J=5.1 Hz, 2H), 8.01 (d, J=7.5 Hz, 1H), 7.63–7.58 (m, 3H), 7.48 (d, J=7.8 Hz, 1H), 7.34–7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 150.2, 143.8, 137.1, 125.3, 123.8, 123.2, 121.8, 121.3, 119.8, 115.6, 112.0; HRMS (ESI) calculated for $C_{13}N_2H_{10}$ ($M+H^+$) requires m/z 195.0922, found m/z 195.0902, HRMS (ESI) calculated for $C_{13}N_2H_{10}$ ($M+Na^+$) requires m/z 217.0742, found m/z 217.0727.

4.3. Nitrosoarene trapping experiment

A mixture of 0.05 mmol Fe(Pc), 5 mmol phenyl acetylene, 5 mmol 2,3-dimethyl-1,3-butadiene, and 15 mL benzene was stirred at reflux under argon and to this was added 0.50 mmol of the *N*-aryl hydroxylamine in 5–6 mL benzene by syringe pump (7–8 h). After the addition was complete, reflux was continued overnight (8–12 h). After cooling, the mixture was evaporated to a solid under vacuum. No indole was detected by GC or by isolation. 4,5-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (**5**) was isolated and the ^{1}H NMR spectrum matched with that reported in the literature.[17b]

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Supplementary data

^{1}H NMR spectra and MS data of all previously reported indoles, as well as ^{1}H and ^{13}C NMR spectra and MS data of all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.004.

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