JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Palladium(II)-Catalyzed Oxidative C−H/C−H Coupling and Eliminative S_N^H Reactions in Direct Functionalization of Imidazole Oxides with Indoles

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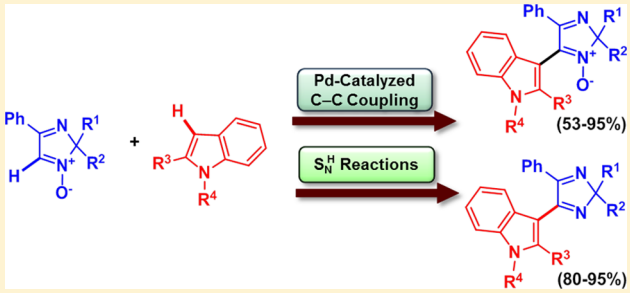
Supporting Information

ABSTRACT: Two novel synthetic approaches to realize the direct C(sp^2)−H bond functionalization in cyclic nitrones are reported. Palladium(II)-catalyzed oxidative C−C coupling of 2,2-dialkyl-4-phenyl-2*H*-imidazole 1-oxides with indoles was shown to result in the formation of 5-indolyl-3-yl derivatives, while nucleophilic substitution of hydrogen (S_N^H) at C(5) of the same imidazole system was found to afford the corresponding deoxygenated compounds.

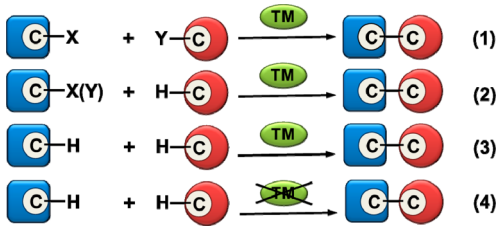


INTRODUCTION

Modern trends in organic synthesis are known to be associated with so-called green chemistry, which prompts development of novel atom efficiency and environmentally benign synthetic methods.[1] In this respect, the formation of new C−C bonds has always been a focus of attention as the key element of diverse synthetic methodologies. From a variety of methods that enable the C−C bond linkage of two organic fragments, e.g., two aromatic or heteroaromatic rings, the well-known cross-coupling reactions, especially those that provide direct C−H functionalization, are elegant and advanced synthetic methodologies (Scheme 1).

Indeed, a huge number of transition metal-catalyzed (Pd, Ni, Cu, etc.) cross-coupling reactions (Suzuki, Negishi, Stille, Kumada, Hiyama, etc.) (mode 1)[2] have found wide applications in laboratory and industrial scale syntheses. The first step in these transformations (mode 1) is based on C−X/C−Y coupling of halides or triflates (X = Hal, OTf) with organoelement compounds bearing the C−Y bond (Y = B, Zn, Sn, Si, Mg, etc.). However, besides metal-complex catalysts, the C−X/C−Y coupling methodology (mode 1) requires a preliminary incorporation of halogen or other auxiliary groups into the starting materials, thus limiting the scope of these reactions. The second type of cross-couplings, the C−X(Y)/C−H (mode 2),[3] is also based on interaction of (pseudo)-halides (X = Hal, OTf, etc.) or organometallics (Y = Mg, Zn, Sn, etc.) with compounds R−H, which do not have to contain any preliminarily introduced functional groups. It should be noted that the next two approaches exploit direct C−H bond functionalization. Because of the innovative character of the C−H/C−H coupling strategies that correspond to the green chemistry principle of atom economy,[1,4] modes 3 and 4[5] were placed at the top positions in the "List of More Aspirational Reactions" of major pharmaceutical companies,[6] as the most advanced methodologies, aimed at reducing human impact on the environment. These transformations can be carried out both catalytically (mode 3) and also without any metal-complex catalysis (mode 4). A great deal of Pd(II)-catalyzed C−H/C−H cross-couplings (mode 3) in a series of aromatic and heteroaromatic compounds have been performed using Ag(I) and Cu(II) as oxidative agents. Nucleophilic substitution of hydrogen (S_N^H), mode 4,[7] does not require any transition metals as catalysts for C−H/C−H couplings. The methodology (mode 4) provides direct nucleophilic C−H functionalization of arenes bearing nitro, cyano, and other electron-withdrawing groups and is effective in a series of π-deficient azaaromatic

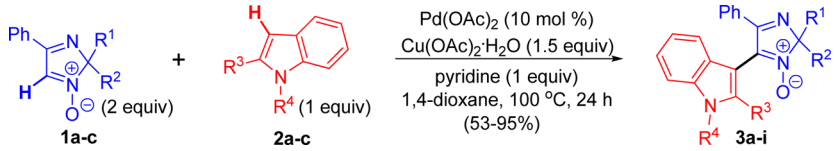
Scheme 1. Principal Strategies for C−C Bond Formation[a]



[a]X = (Pseudo)halides; Y = organometallics; TM = transition metal catalyst.

Received: July 31, 2012
Published: September 21, 2012

Scheme 2. Palladium(II)-Catalyzed Oxidative Coupling of Imidazole Nitrones 1a−c with Indoles 2a−c



compounds, such as azines and their N-activated forms (*N*-oxides, quaternary salts, etc.).[7]

Although the C−H/C−H coupling methodologies (modes 3 and 4) have been extensively used to modify arenes, azines, and azoles, no examples of C−H functionalization in a series of nonaromatic heterocyclic compounds, e.g., 2,2-dialkyl-substituted imidazole 1-oxides, have been reported in the literature so far. Meanwhile, nitrones are of interest for many practical applications. Indeed, these derivatives[8] are known as biologically active substances, precursors for stable nitroxide radicals, free radical traps, stabilizers of polymers, light-sensitive additives, and also as other components of advanced materials.

The paper is focused upon the development of new synthetic approaches to C-substituted azomethine derivatives using both catalytic and noncatalytic C−H/C−H cross-coupling reactions of cyclic nitrones with indoles. The latter were chosen because their fragments are presented well in various organic compounds used in pharmaceutical and fragrance industries, materials science, agriculture, etc.[9]

RESULTS AND DISCUSSION

Cyclic nitrones,[10] bearing an azadiene fragment and a hydrogen atom at the α-position to the N^+-O^- group, can be regarded as nonaromatic analogues of azine *N*-oxides. The latter are known to undergo Pd-catalyzed oxidative C−C coupling reactions with a wide range of five-membered heteroaromatic compounds such as indoles, pyrroles, thiophenes, and others.[11] To estimate the scope of the C−H/C−H cross-coupling reactions, for the first time we have extended our studies to the chemistry of nonaromatic compounds and have attempted to realize the C−C coupling of imidazole nitrones **1a−c** with indoles **2a−c** (Scheme 2). The reactions were carried out in 1,4-dioxane in the presence of pyridine (base), palladium(II) acetate (catalyst), and copper(II) acetate (oxidant) to give the C−C coupling products **3a−i** with the retention of the *N*-oxide function in the imidazole ring in moderate-to-good yields.

To optimize the reaction conditions, a series of experiments have been performed. Yields of compounds **3a−i** proved to depend on the reaction time (Table 1.1), ratio of reagents (Table 1.2), and quantities of catalyst (Table 1.3) and oxidant (Table 1.4). The C−C coupling of bicyclic imidazole nitrone **1c** with *N*-methylindole **2b**, leading to **3h**, has been chosen as the model reaction. The data obtained indicate that optimal conditions, providing the best yields of products **3a−i**, can be achieved by refluxing the reaction mixture in 1,4-dioxane for 24 h (Table 1, entry 1.3) using the following ratio of reagents: nitrone (2 equiv), indole (1 equiv) (Table 1, entry 2.4), $Pd(OAc)_2$ (0.1 equiv) (Table 1, entry 3.3), and $Cu(OAc)_2·H_2O$ (1.5 equiv) (Table 1, entry 4.3). Yields of synthesized indolyl-substituted nitrones are given in Table 2.

As mentioned above, the cross-coupling of **1a−c** with **2a−c** can be accomplished in the presence of Pd(II) acetate. Attempts to use acetates of other transition metals, such as $Ni(OAc)_2$ and $Co(OAc)_2$, under the same reaction conditions were unsuccessful, with only starting materials and their decomposition products being found in the reaction mixtures. The choice of Ni(II) and Co(II) catalysts for testing is due to

Table 1. Optimization of the Reaction Conditions for Palladium(II)-Catalyzed Oxidative Coupling of Imidazole Nitrones 1b with Indoles 2c

1. Yields of Compound **3h** Depending on the Reaction Time		
entry	reaction time (h)	yield (%)
1.1	6	63
1.2	12	76
1.3	24	95
1.4	36	82
1.5	48	77

2. Yields of Compound **3h** Depending on the Ratio of Reagents			
entry	nitrone **1b** (equiv)	indole **2c** (equiv)	yield (%)
2.1	1	4	78
2.2	1	2	80
2.3	1	1	85
2.4	2	1	95
2.5	4	1	92

3. Yields of Compound **3h** Depending on Quantity of $Pd(OAc)_2$		
entry	$Pd(OAc)_2$ (mol %)	yield (%)
3.1	2	45
3.2	5	75
3.3	10	95
3.4	15	95
3.5	20	92

4. Yields of Compound **3h** Depending on Quantity of $Cu(OAc)_2$		
entry	$Cu(OAc)_2$ (equiv)	yield (%)
4.1	0.5	35
4.2	1	70
4.3	1.5	95
4.4	2	95
4.5	2.5	82

Table 2. Yields of Compounds 3a−i

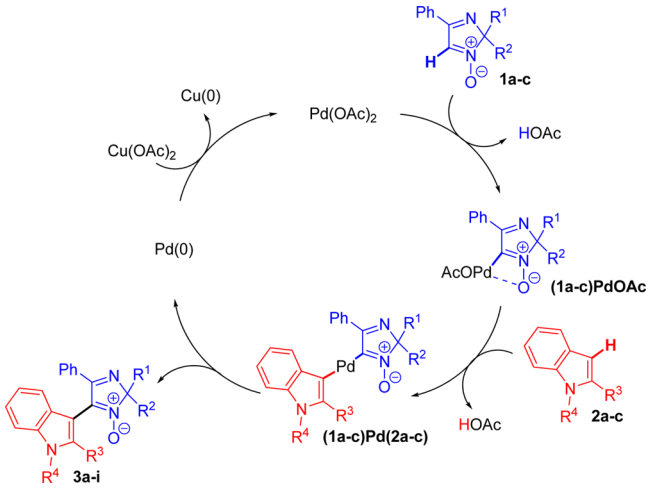
entry	nitrone **1**	indole **2**	product **3**	yield (%)
1	$R^1 = R^2 =$ Me (**1a**)	$R^3 = R^4 =$ H (**2a**)	**3a**	53
2	$R^1 = R^2 =$ Me (**1a**)	$R^3 =$ H, $R^4 =$ Me (**2b**)	**3b**	88
3	$R^1 = R^2 =$ Me (**1a**)	$R^3 =$ Me, $R^4 =$ H (**2c**)	**3c**	65
4	$R^1 =$ Me, $R^2 =$ Et (**1b**)	$R^3 = R^4 =$ H (**2a**)	**3d**	53
5	$R^1 =$ Me, $R^2 =$ Et (**1b**)	$R^3 =$ H, $R^4 =$ Me (**2b**)	**3e**	92
6	$R^1 =$ Me, $R^2 =$ Et (**1b**)	$R^3 =$ Me, $R^4 =$ H (**2c**)	**3f**	84
7	$R^1 = R^2 = (CH_2)_5$ (**1c**)	$R^3 = R^4 =$ H (**2a**)	**3g**	55
8	$R^1 = R^2 = (CH_2)_5$ (**1c**)	$R^3 =$ H, $R^4 =$ Me (**2b**)	**3h**	95
9	$R^1 = R^2 = (CH_2)_5$ (**1c**)	$R^3 =$ Me, $R^4 =$ H (**2c**)	**3i**	83

dx.doi.org/10.1021/jo301618b | J. Org. Chem. 2012, 77, 9087−9093

previous good results with their use in the direct C−H bond functionalization of heterocycles.[3h,i,12]

The C−C bond formation in the C−H/C−H coupling reactions without any catalyst was previously stated to be thermodynamically unfavorable.[13] However, the activation energy can be considerably decreased by using an appropriate catalyst and an oxidant. According to the current concept, the oxidative C−H/C−H coupling is a cyclic process involving Pd(II) redox transformations. The most plausible mechanism for describing these interactions has been proposed on the basis of the literature data (Scheme 3).[5h,14] In the first stage,

Scheme 3. Plausible Catalytic Cycle for the Oxidative C−H/C−H Cross-Coupling of Imidazole 1-Oxides 1a−c with Indoles 2a−c



$Pd(OAc)_2$ reacts with imidazole nitrones **1a−c**, activating the $C(sp^2)$−H bond[14a,15] in the azomethine fragment. The C−H bond cleavage is supposed to occur at the cyclopalladation step,[16] thus resulting in organopalladium intermediates (**1a−c**)PdOAc. The intramolecular Pd···O^-−N^+ bond formation facilitates the C−H activation. In other words, the complex-induced proximity effect (CIPE)[17] of the *N*-oxide moiety may be of great importance for these transformations. Interaction of (**1a−c**)PdOAc with indoles **2a−c** affords organometallic compounds (**1a−c**)Pd(**2a−c**) which are transformed into the corresponding C−C coupling products **3a−i** and Pd(0). Herein, Cu(II) is regarded as an oxidant for conversion of Pd(0) into Pd(II), recovering the latter as acetate for the next catalytic cycle. Thus, the suggested mechanism is likely to describe the C−H/C−H coupling process in a simplified form, while it has previously been postulated as a thermodynamically unfavorable one.

Another approach to cause the direct C−H functionalization of imidazole is substitution of hydrogen (S_N^H) in nitrones **1a−c** by action of nucleophilic indoles **2a−c**. The methodology allows C−H/C−H coupling products to be obtained *under very mild* reaction *conditions without any transition metal catalysis*.[7] It has been established that nucleophilic attack of indoles **2a−c** at unsubstituted carbon C(5) of imidazole 1-oxide **1a−c** takes place in the presence of acetyl chloride (Scheme 4) and results in the formation of heterocyclic derivatives **4a−i**, which can be regarded as deoxygenated analogues of compounds **3a−i** (Table 3). Compared with Pd-catalyzed cross-coupling

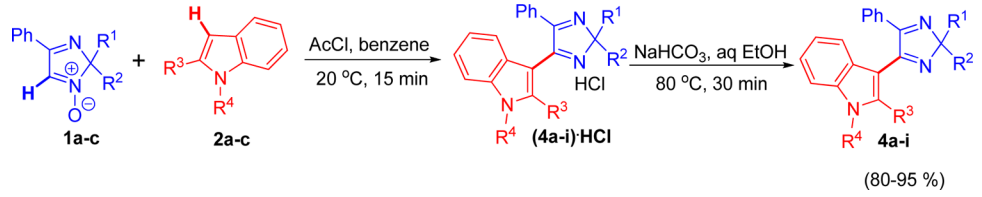
Table 3. Yields of Compounds 4a−i

entry	nitrone **1**	indole **2**	product **4a−i**	yield (%)
1	$R^1 = R^2$ = Me (**1a**)	$R^3 = R^4$ = H (**2a**)	**4a**	90
2	$R^1 = R^2$ = Me(**1a**)	R^3 = H, R^4 = Me (**2b**)	**4b**	85
3	$R^1 = R^2$ = Me (**1a**)	R^3 = Me, R^4 = H (**2c**)	**4c**	92
4	R^1 = Me, R^2 = Et (**1b**)	$R^3 = R^4$ = H (**2a**)	**4d**	84
5	R^1 = Me, R^2 = Et (**1b**)	R^3 = H, R^4 = Me (**2b**)	**4e**	82
6	R^1 = Me, R^2 = Et (**1b**)	R^3 = Me, R^4 = H (**2c**)	**4f**	90
7	$R^1 = R^2 = (CH_2)_5$ (**1c**)	$R^3 = R^4$ = H (**2a**)	**4g**	90
8	$R^1 = R^2 = (CH_2)_5$ (**1c**)	R^3 = H, R^4 = Me (**2b**)	**4h**	82
9	$R^1 = R^2 = (CH_2)_5$ (**1c**)	R^3 = Me, R^4 = H (**2c**)	**4i**	88

(Scheme 2), the S_N^H reaction is a faster process, taking only a few minutes (contrary to refluxing 24 h in 1,4-dioxane). Moreover, the presented synthetic approach is characterized by the simplicity in isolation and purification of the products (**4a−i**)·HCl. Indeed, unlike the starting materials **1a−c** and **2a−c**, hydrochlorides (**4a−i**)·HCl possess a limited solubility in nonpolar solvents (benzene, toluene, hexane), and therefore they are fully precipitated from the reaction solutions. The subsequent hydrolysis of the salts (**4a−i**)·HCl with $NaHCO_3$ in aqueous ethanol affords indolyl-substituted imidazoles **4a−i** in good yields, 80−95%.

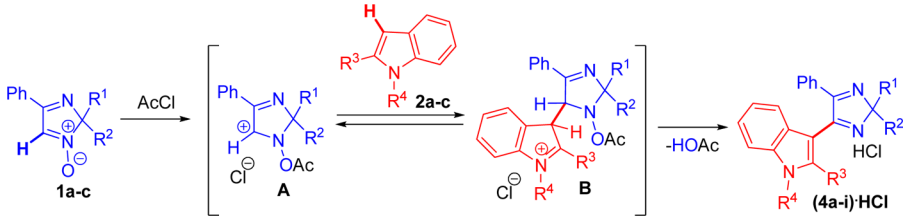
According to the common concept,[7] the S_N^H reactions proceed via two (addition−elimination) steps. In the first stage, an addition of nucleophilic indoles **2a−c** to the activated nitrones **A** occurs, with the short-lived σ^H-adducts **B** being formed (Scheme 5). Elimination of acetic acid from intermediate **B**, in the second step, leads to S_N^H products in the form of hydrochlorides (**4a−i**)·HCl. Their precipitation from reaction solutions shifts the dynamic equilibrium toward the direct reaction, thus providing good yields of indolyl-substituted imidazoles **4a−i**. The observed C−H functionalization of imidazole *N*-oxides, which do not contain a cyclic π-conjugated system, is a quite rare example of the S_N^H reactions in nonaromatic heterocycles.

Scheme 4. S_N^H Coupling of Nitrones 1a−c with Indoles 2a−c

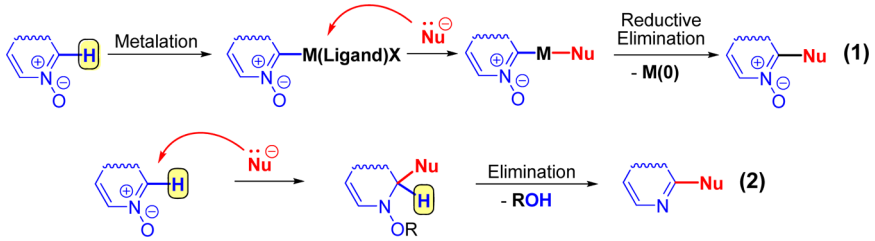


dx.doi.org/10.1021/jo301618b | J. Org. Chem. 2012, 77, 9087−9093

Scheme 5. Plausible Mechanism for Noncatalytic S_N^H Transformation of Imidazole 1-Oxides 1a–c by the Action of Indoles 2a–c



Scheme 6. Nucleophilic "Addition–Elimination" Protocol: Catalytic Activation of C–H Bond (1) and Activation of π-System for Nucleophilic Attack (2)



The compounds **3a–i** and **4a–i** were characterized by ^{1}H and ^{13}C NMR and IR spectroscopy, mass spectrometry, and elemental analysis. The X-ray diffraction studies for compounds **3b** and **4e** were also carried out. The values of bond lengths and bond angles in both cases are close to standard ones.[18] The obtained data are given in the Supporting Information. The ^{1}H and ^{13}C NMR spectra[19] proved to be in full correspondence with the structures. In particular, the ^{1}H NMR spectra of compounds **3a,c,d,f,g,i** and **4a,c,d,f,g,i** contain the N–H signals at δ 11.19–11.59 ppm, which diminish after addition of CF_3COOD. All mass spectra have peaks of molecular ions $[M + H]^+$, and in the case of imidazole *N*-oxides **3a–i** the $[M + H]^+$ are 16 amu higher than those for their deoxygenated analogues **4a–i**. Absorption bands, corresponding to the stretching vibrations of N–H groups at ν 3120–3270 cm^{-1}, are also presented in the IR spectra of **3a,c,d,f,g,i** and **4a,c,d,f,g,i**.

CONCLUSIONS

In summary, two synthetic approaches to new heterocyclic compounds, bearing imidazole and indole fragments linked to each other, have been advanced. Both methods exploit nucleophilic C–H bond functionalization that is realized either via the palladium(II)-catalyzed oxidative C–C cross-coupling reaction (1) or by nucleophilic substitution of hydrogen (S_N^H) without any metal catalysis (2) (Scheme 6).

The features of the palladium(II)-catalyzed C–H bond activation (Scheme 6.1) are the following: (a) in the first step, action of a base on the *N*-oxide causes the hydrogen atom to leave as a proton and results in the organometallic compound; (b) in the second stage, interaction of the latter with a nucleophilic reagent takes place; (c) as a result of reductive elimination, the C–C coupling product is formed, with M(II) being reduced to M(0) (the "metalation–nucleophilic addition–reductive elimination" protocol). Meanwhile, the S_N^H approach is based on a direct nucleophilic attack at the unsubstituted carbon of the cyclic π-conjugated system (Scheme 6.2) to give σ^H-adducts followed by elimination of a proton with the auxiliary group (the "nucleophilic addition–elimination" protocol). In conclusion, the new imidazoles obtained may be of interest as potential biologically active compounds, free radical traps, ligands for complexations with metals, and precursors for stable nitroxide radicals.

EXPERIMENTAL SECTION

Synthesis of 2-Ethyl-2-methyl-4-phenyl-2*H*-imidazole 1-Oxide (1b). A mixture of (*E*)-2-oxo-2-phenylacetaldehyde oxime (1.49 g, 0.01 mol), butan-2-one (6.26 mL, 0.12 mol), NH_4OAc (4.62 g, 0.06 mol), and glacial acetic acid (6.86 mL, 0.12 mol) was heated under reflux for 2 h. The reaction mixture was cooled, and water (500 mL) was added. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by recrystallization from heptane. Yield 279 mg (85%), mp 68–70 °C, R_f 0.2 ($CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 8.30 (s, 1H), 8.11–7.86 (m, 2H), 7.66–7.38 (m, 3H), 2.06 (dq, J = 14.6, 7.3 Hz, 1H), 1.86 (dq, J = 14.6, 7.3 Hz, 1H), 1.50 (s, 3H), 0.63 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) ppm: δ 165.6, 131.8, 130.9, 129.0, 127.3, 126.6, 103.6, 29.9, 23.4, 6.8. IR (DRA): 3080, 2984, 2934, 1543, 1570, 1510, 1441, 1418, 1323, 1233, 1177, 1116, 965, 844 cm^{-1}. MS (ESI): m/z 203 $[M + H]^+$. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.33; H, 7.03; N, 13.68.

General Procedure for the Synthesis of 3a–i. A mixture of corresponding nitrone **1a–c** (2 mmol), indole **2a–c** (1 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), $Cu(OAc)_2·H_2O$ (450 mg, 1.5 mmol), and pyridine (0.08 mL, 1 mmol) in 1,4-dioxane (10 mL) was heated at 110 °C for 24 h. The reaction mixture was cooled to room temperature, filtered through neutral alumina, and concentrated in vacuo. The residue was subjected to silica gel column chromatography with the EtOAc–hexane mixture as an eluent, and the resulting eluate was concentrated to dryness under reduced pressure.

*5-(1H-Indol-3-yl)-2,2-dimethyl-4-phenyl-2H-imidazole 1-Oxide (**3a**).* Yield 161 mg (53%), mp 120–122 °C, R_f 0.2 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.58 (m, 1H, J = 7.4 Hz), 7.76 (d, J = 2.6 Hz, 1H), 7.62 (m, 2H), 7.51–7.29 (m, 4H), 7.04 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.76 (t, J = 7.5 Hz, 1H), 1.61 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 166.1, 135.8, 133.2, 132.0, 130.6, 128.5, 128.4, 128.0, 124.7, 121.8, 121.2, 119.4, 112.0, 101.3, 98.4, 24.6. IR (DRA): 3123, 3098, 2914, 2854, 1568, 1540, 1510, 1471, 1435, 1370, 1236, 1210, 950, 780 cm^{-1}. MS (ESI): m/z 304 $[M + H]^+$. Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.03; H, 5.65; N, 13.64.

dx.doi.org/10.1021/jo301618b | J. Org. Chem. 2012, 77, 9087–9093

*2,2-Dimethyl-5-(1-methyl-1H-indol-3-yl)-4-phenyl-2H-imidazole 1-Oxide (**3b**).* Yield 279 mg (88%), mp 164−167 °C, R_f 0.3 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 7.91 (s, 1H), 7.66−7.57 (m, 2H), 7.50−7.36 (m, 2H), 7.33 (m, 2H), 7.10 (dd, J = 11.1, 4.0 Hz, 1H), 6.83−6.69 (m, 2H), 3.88 (s, 3H), 1.61 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 165.9, 136.3, 133.2, 132.5, 131.5, 130.6, 128.5, 128.0, 125.0, 121.8, 121.2, 119.6, 110.3, 100.3, 98.4, 32.9, 24.6. IR (DRA): 2981, 2931, 1573, 1548, 1511, 1461, 1408, 1330, 1238, 1173, 1151, 1116, 1006, 945, 776 cm^{-1}. MS (ESI): m/z 318 [M + H]$^+$. Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.76; H, 6.08; N, 13.07. The crystallographic data is presented in Supporting Information and is available from the Cambridge Crystallographic Data Centre at http://www.ccdc.cam.ac.uk/data_request/cif (deposition no. CCDC 889116).

*2,2-Dimethyl-5-(2-methyl-1H-indol-3-yl)-4-phenyl-2H-imidazole 1-Oxide (**3c**).* Yield 207 mg (65%), mp 190−193 °C, R_f 0.25 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.37 (s, 1H), 7.62 (m, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.28 (m, 3H), 6.98 (m, 1H), 6.77 (m, 2H), 2.17 (s, 3H), 1.62 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 165.8, 137.7, 135.5, 132.8, 132.1, 130.7, 128.4, 128.3, 127.5, 126.4, 120.9, 119.3, 119.0, 111.1, 98.5, 24.9, 13.3. IR (DRA): 3214, 3191, 2996, 1577, 1557, 1512, 1447, 1382, 1336, 1232, 1173, 1013, 923 cm^{-1}. MS (ESI): m/z 318 [M + H]$^+$. Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.88; H, 6.28; N, 12.98.

*2-Ethyl-5-(1H-indol-3-yl)-2-methyl-4-phenyl-2H-imidazole 1-Oxide (**3d**).* Yield 168 mg (53%), mp 85−88 °C, R_f 0.25 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.59 (m, 1H), 7.71 (d, J = 2.8 Hz, 1H), 7.61 (d, 2H), 7.49−7.30 (m, 4H), 7.05 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 2.14 (dq, J = 14.3, 7.2 Hz, 1H), 2.00 (dq, J = 14.4, 7.2 Hz, 1H), 1.61 (s, 3H), 0.67 (t, J = 7.3 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 167.1, 135.8, 133.3, 133.1, 130.6, 128.5, 128.4, 128.0, 124.8, 121.8, 121.1, 119.4, 112.0, 101.1, 100.7, 30.2, 23.8, 6.8. IR (DRA): 3187, 3087, 2917, 2854, 1570, 1544, 1512, 1481, 1433, 1366, 1228, 1212, 952, 783 cm^{-1}. MS (ESI): m/z 318 [M + H]$^+$. Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.43; H, 6.33; N, 13.24.

*2-Ethyl-2-methyl-5-(1-methyl-1H-indol-3-yl)-4-phenyl-2H-imidazole 1-Oxide (**3e**).* Yield 305 mg (92%), mp 125−128 °C, R_f 0.3 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 7.88 (s, 1H), 7.62 (m, 2H), 7.49−7.38 (m, 2H), 7.33 (m, 2H), 7.11 (m, 1H), 6.80 (m, 2H), 3.88 (s, 3H), 2.14 (dq, J = 14.5, 7.3 Hz, 1H), 2.00 (dq, J = 14.5, 7.3 Hz, 1H), 1.61 (s, 3H), 0.65 (t, J = 7.3 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 167.0, 136.3, 133.0, 132.4, 130.7, 128.5, 127.9, 125.1, 121.8, 121.0, 119.6, 110.4, 100.8, 100.1, 65.0, 32.9, 30.2, 23.8, 6.7. IR (DRA): 2991, 2965, 2923, 1725, 1568, 1511, 1463, 1427, 1284, 1220, 1132, 950, 824 cm^{-1}. MS (ESI): m/z 332 [M + H]$^+$. Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 76.33; H, 6.56; N, 12.58.

*2-Ethyl-2-methyl-5-(2-methyl-1H-indol-3-yl)-4-phenyl-2H-imidazole 1-Oxide (**3f**).* Yield 278 mg (84%), mp 169−172 °C, R_f 0.3 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.37 (s, 1H), 7.62 (m, 2H), 7.38 (m, 1H), 7.32−7.23 (m, 3H), 6.97 (s, 1H), 6.82−6.71 (m, 2H), 2.16 (m, 4H), 2.02 (m, 1H), 1.62 (d, J = 8.3 Hz, 3H), 0.68 (m, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 166.9, 137.7, 135.5, 133.5, 132.7, 130.7, 128.4, 127.4, 126.5, 120.8, 119.3, 119.0, 118.6, 111.1, 100.9, 30.0, 24.1, 13.2, 6.7. IR (DRA): 3213, 3059, 1574, 1510, 1445, 1341, 1228, 1086, 951, 751 cm^{-1}. MS (ESI): m/z 332 [M + H]$^+$. Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 76.33; H, 6.23; N, 12.48.

*2-(1H-Indol-3-yl)-3-phenyl-1,4-diazaspiro[4.5]deca-1,3-diene 1-Oxide (**3g**).* Yield 189 mg (55%), mp 180−182 °C, R_f 0.25 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.59 (m, 1H), 7.78 (d, J = 2.8 Hz, 1H), 7.62 (m, 2H), 7.33−7.45 (m, 4H), 7.03 (t, J = 7.0 Hz, 1H), 6.84−6.71 (m, 2H), 2.21−2.07 (m, 2H), 2.01−1.86 (m, 5H), 1.47 (m, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 166.4, 135.8, 133.4, 132.1, 130.5, 128.5, 128.4, 128.1, 124.7, 121.7, 121.2, 119.3, 111.9, 101.2, 100.7, 35.0, 24.6, 23.0. IR (DRA): 3226, 3142, 2932, 2857, 1569, 1511, 1499, 1434,1388, 1298, 1242, 989, 778 cm^{-1}. MS (ESI): m/z 344 [M + H]$^+$. Anal. Calcd for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 76.89; H, 6.08; N, 12.45.

*2-(1-Methyl-1H-indol-3-yl)-3-phenyl-1,4-diazaspiro[4.5]deca-1,3-diene 1-Oxide (**3h**).* Yield 339 mg (95%), mp 165−167 °C, R_f 0.25 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 7.94 (s, 1H), 7.63 (m, 2H), 7.50−7.37 (m, 2H), 7.33 (m, 2H), 7.10 (t, J = 7.4 Hz, 1H), 6.77 (t, J = 7.5 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 2.22−2.07 (m, 2H), 2.03−1.84 (m, 5H), 1.46 (m, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 166.2, 136.3, 133.4, 132.6, 131.7, 130.5, 128.4, 128.0, 125.0, 121.8, 121.1, 119.5, 110.3, 100.7, 100.2, 35.0, 32.9, 24.5, 23.0. IR (DRA): 2935, 2859,1573, 1511, 1497, 1371, 1297, 1178, 1113, 829, 766 cm^{-1}. MS (ESI): m/z 358 [M + H]$^+$. Anal. Calcd for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.76. Found: C, 77.28; H, 6.60; N, 11.76.

*2-(2-Methyl-1H-indol-3-yl)-3-phenyl-1,4-diazaspiro[4.5]deca-1,3-diene 1-Oxide (**3i**).* Yield 296 mg (83%), mp 256−260 °C, R_f 0.2 (hexane/EtOAc, 6:4). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.32 (s, 1H), 7.68−7.60 (m, 2H), 7.38 (m, 1H), 7.31−7.21 (m, 3H), 6.99 (m, 1H), 6.78 (m, 2H), 2.21−2.11 (m, 5H), 2.03−1.87 (m, 5H), 1.54−1.42 (m, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 166.1, 137.7, 135.5, 133.0, 132.3, 130.6, 128.4, 127.5, 126.4, 120.8, 119.3, 119.0, 111.1, 100.7, 98.6, 35.3, 24.6, 23.0, 13.2. IR (DRA): 3266, 3058, 2946, 2923, 2858, 1570, 1551, 1510, 1482, 1446, 1311, 1167, 778 cm^{-1}. MS (ESI): m/z 358 [M + H]$^+$. Anal. Calcd for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.76. Found: C, 77.51; H, 6.49; N, 11.58.

General Procedure for the Synthesis of 4a−i. To a stirring solution of the corresponding nitrone **1a−c** (1 mmol) and indole **2a−c** (1 mmol) in benzene (15 mL), AcCl (0.07 mL, 1 mmol) was added dropwise at 5 °C. After 5 min, the reaction mixture was warmed to room temperature, and formed precipitate of (**4a−i**)·HCl was filtered off, washed with benzene, and dried in air for 24 h. Then, to the suspension of the corresponding (**4a−i**)·HCl in EtOH (20 mL) was added 10% aq solution of $NaHCO_3$ (1.25 mL, 1.5 mmol), and the mixture was heated under reflux for 30 min. Finally, the reaction mixture was cooled and filtered through silica gel and concentrated in vacuo. The residue was purified by recrystallization from the heptane−benzene mixture.

*3-(2,2-Dimethyl-5-phenyl-2H-imidazol-4-yl)-1H-indole (**4a**).* Yield 250 mg (90%), mp 255−258 °C, R_f 0.3 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.22 (m, 1H), 8.26 (d, J = 7.7 Hz, 1H), 7.61−7.55 (m, 2H), 7.55−7.45 (m, 3H), 7.37 (d, J = 7.7 Hz, 1H), 7.18−7.05 (m, 2H), 6.89 (d, J = 2.8 Hz, 1H), 1.57 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 164.8, 158.1, 136.1, 134.6, 129.6, 128.5, 128.4, 128.3, 126.4, 122.7, 122.0, 120.6, 111.8, 108.0, 101.4, 24.8. IR (DRA): 3205, 3110, 2932, 2752, 1599, 1570, 1510, 1442, 1178, 1138, 1034, 1006, 935, 785 cm^{-1}. MS (ESI): m/z 288 [M + H]$^+$. Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.61; H, 6.00; N, 14.44.

*3-(2,2-Dimethyl-5-phenyl-2H-imidazol-4-yl)-1-methyl-1H-indole (**4b**).* Yield 256 mg (85%), mp 98−100 °C, R_f 0.3 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 8.24 (d, J = 7.9 Hz, 1H), 7.63−7.44 (m, 5H), 7.38 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 6.86 (s, 1H), 3.70 (s, 3H), 1.56 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 164.6, 157.7, 136.7, 134.2, 132.2, 129.8, 128.4, 128.3, 126.8, 122.8, 122.1, 120.8, 110.2, 107.1, 101.3, 32.9, 24.8. IR (DRA): 2990, 2927, 2826, 1599, 1570, 1509, 1444, 1340, 1257, 1163, 1098, 1163, 921, 747 cm^{-1}. MS (ESI): m/z 302 [M + H]$^+$. Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.72; H, 6.24; N, 14.04.

*3-(2,2-Dimethyl-5-phenyl-2H-imidazol-4-yl)-2-methyl-1H-indole (**4c**).* Yield 277 mg (92%), mp 174−177 °C, R_f 0.25 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.20 (s, 1H), 7.57−7.49 (m, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.26 (m, 3H), 7.03 (d, J = 7.9 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.78 (t, J = 7.2 Hz, 1H), 2.13 (s, 3H), 1.58 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 164.3, 159.3, 136.9, 135.2, 133.2, 129.9, 128.3, 128.0, 127.1, 121.0, 119.3, 119.1, 110.8, 105.4, 101.2, 24.6, 12.6. IR (DRA): 3204, 3068, 2930, 2869, 1602, 1574, 1510, 1428, 1271, 1200, 1013, 938, 748 cm^{-1}.

dx.doi.org/10.1021/jo301618b | J. Org. Chem. 2012, 77, 9087−9093

MS (ESI): m/z 302 $[M + H]^+$. Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.67; H, 6.52; N, 13.84.

*3-(2-Ethyl-2-methyl-5-phenyl-2H-imidazol-4-yl)-1H-indole (**4d**).* Yield 253 mg (84%), mp 245−248 °C, R_f 0.2 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.26 (m, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.60−7.46 (m, 5H), 7.38 (d, J = 7.9 Hz, 1H), 7.19−7.06 (m, 2H), 6.89 (d, J = 2.9 Hz, 1H), 2.05 (qq, J = 14.5, 7.3 Hz, 2H), 1.54 (s, 3H), 0.79 (t, J = 7.3 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 165.5, 158.6, 136.1, 134.7, 129.6, 128.4, 128.4, 128.3, 126.5, 122.7, 122.0, 120.7, 111.8, 108.0, 103.6, 30.9, 23.2, 8.4. IR (DRA): 3141, 3104, 2972, 2877, 1599, 1566, 1509, 1494, 1364, 1258, 1246, 1140, 997, 878, 750 cm^{-1}. MS (ESI): m/z 302 $[M + H]^+$. Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.83; H, 6.33; N, 13.96.

*3-(2-Ethyl-2-methyl-5-phenyl-2H-imidazol-4-yl)-1-methyl-1H-indole (**4e**).* Yield 258 mg (82%), mp 100−102 °C, R_f 0.25 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 8.23 (d, J = 7.8 Hz, 1H), 7.60−7.45 (m, 5H), 7.38 (d, J = 8.2 Hz, 1H), 7.22 (m, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.87 (s, 1H), 3.70 (s, 3H), 2.15−1.96 (m, 2H), 1.55 (s, 3H), 0.78 (t, J = 7.3 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 165.2, 158.2, 136.7, 134.3, 132.1, 129.7, 128.4, 128.3, 126.9, 122.7, 122.0, 120.8, 110.2, 107.1, 103.5, 32.8, 30.8, 23.2, 8.3. IR (DRA): 2971, 2875, 1559, 1510, 1463, 1446, 1340, 1297, 1098, 1007, 908, 736 cm^{-1}. MS (ESI): m/z 316 $[M + H]^+$. Anal. Calcd for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.96; H, 6.86; N, 13.25. The crystallographic data is presented in Supporting Information and is available from the Cambridge Crystallographic Data Centre at http://www.ccdc.cam.ac.uk/data_request/cif (deposition no. CCDC 889117).

*3-(2-Ethyl-2-methyl-5-phenyl-2H-imidazol-4-yl)-2-methyl-1H-indole (**4f**).* Yield: 283 mg (90%), mp 182−185 °C, R_f 0.25 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.22 (s, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.42−7.23 (m, 4H), 7.03 (d, J = 7.9 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.79 (t, J = 7.5 Hz, 1H), 2.13−2.04 (m, 5H), 1.56 (s, 3H), 0.76 (t, J = 7.3 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 165.1, 160.0, 136.7, 135.3, 133.2, 129.9, 128.3, 127.9, 127.20, 121.0, 119.4, 119.0, 110.9, 105.5, 103.5, 30.5, 23.3, 12.6, 8.2. IR (DRA): 3163, 3064, 2927, 1575, 1510, 1490, 1427, 1310, 1185, 1008, 975, 738 cm^{-1}. MS (ESI): m/z 316 $[M + H]^+$. Anal. Calcd for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.96; H, 6.87; N, 13.06.

*3-(3-Phenyl-1,4-diazaspiro[4.5]deca-1,3-dien-2-yl)-1H-indole (**4g**).* Yield 294 mg (90%), mp 240−244 °C, R_f 0.2 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.19 (m, 1H), 8.27 (d, J = 7.3 Hz, 1H), 7.60−7.55 (m, 2H), 7.54−7.44 (m, 3H), 7.37 (d, J = 7.5 Hz, 1H), 7.12 (m, 2H), 6.90 (d, J = 2.8 Hz, 1H), 2.11−1.84 (m, 4H), 1.83−1.58 (m, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 164.9, 158.0, 136.1, 134.9, 129.6, 128.4, 128.4, 126.4, 122.7, 122.1, 120.7, 111.8, 108.2, 103.5, 35.0, 25.4, 24.0. IR (DRA): 3149, 3066, 2987, 2858, 1562, 1510, 1447, 1175, 1105, 1008, 979, 765, cm^{-1}. MS (ESI): m/z 328 $[M + H]^+$. Anal. Calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.46; N, 12.83. Found: C, 80.81; H, 6.41; N, 12.80.

*1-Methyl-3-(3-phenyl-1,4-diazaspiro[4.5]deca-1,3-dien-2-yl)-1H-indole (**4h**).* Yield 258 mg (82%), mp 130−132 °C. R_f 0.25 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 8.27 (d, J = 7.8 Hz, 1H), 7.61−7.56 (m, 2H), 7.55−7.45 (m, 3H), 7.37 (d, J = 8.1 Hz, 1H), 7.23 (m, 1H), 7.15 (m, 1H), 6.88 (s, 1H), 3.70 (s, 3H), 2.05−1.86 (m, 4H), 1.81−1.62 (m, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 164.6, 157.6, 136.7, 134.5, 132.0, 129.7, 128.4, 128.4, 126.8, 122.7, 122.2, 120.9, 110.2, 107.4, 103.4, 35.0, 32.9, 25.4, 24.0. IR (DRA): 2927, 2855, 1599, 1566, 1510, 1446, 1369, 1336, 1220, 1096, 1009, 953, 902, 738 cm^{-1}. MS (ESI): m/z 342 $[M + H]^+$. Anal. Calcd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 81.12; H, 6.98; N, 12.21.

*2-Methyl-3-(3-phenyl-1,4-diazaspiro[4.5]deca-1,3-dien-2-yl)-1H-indole (**4i**).* Yield 300 mg (88%), mp 216−220 °C, R_f 0.2 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1) ppm: δ 11.20 (s, 1H), 7.54 (m, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.26 (m, 3H), 7.03 (d, J = 7.9 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.79 (t, J = 7.4 Hz, 1H), 2.11 (s, 3H), 1.98−1.88 (m, 4H), 1.79−1.65 (m, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) ppm: δ 164.3, 159.3, 136.8, 135.3, 133.4, 129.8, 128.3, 128.0, 127.2, 121.0, 119.3, 119.1, 110.8, 105.8, 103.4, 35.0, 25.3, 23.9, 12.6. IR (DRA): 3245, 3173, 3073, 2977, 2852, 1901, 1573, 1516, 1488, 1422, 1300, 1249, 1300, 1189, 1008, 849 cm^{-1}. MS (ESI): m/z 342 $[M + H]^+$. Anal. Calcd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 81.03; H, 7.01; N, 12.21.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental methods, copies of NMR (^{1}H and ^{13}C) spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The spectral data were obtained at the "Integrated research and expert assessment of organic materials" laboratory (Ural Federal University). The research was financially supported by the Council on Grants of the President of the Russian Federation (Program for State Support of Leading Scientific Schools of the Russian Federation, Grant NSh-5505.2012.3), the Russian Foundation for Basic Research (Project no. 10-03-00756-a), the Civilian Research and Development Foundation (CRDF REC 005), and the Ural Federal University development program with financial support of young scientists.

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