Symmetrical Nitroxide Synthesis: Meso versus *d,l* Diastereomer Formation

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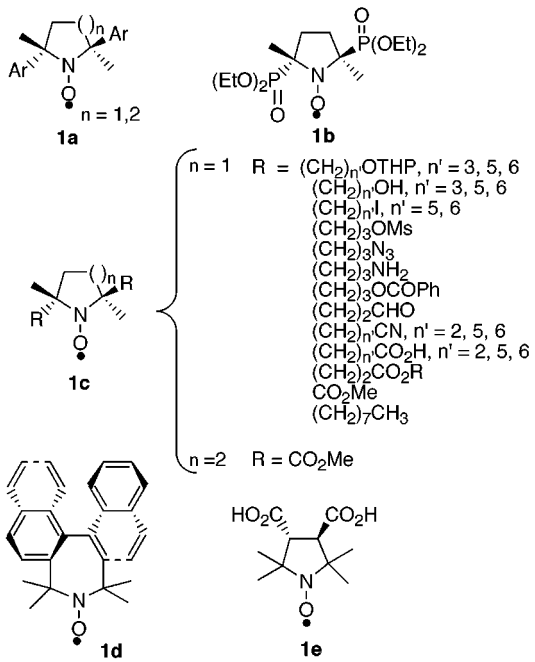
Received August 7, 1998

The syntheses of C_2-symmetrical isoindoline nitroxide **2a** and *meso*-isoindoline nitroxide **2b** have been achieved by two different routes. The chiral C_2-symmetric nitroxide derives from the addition of a Grignard reagent from the least hindered face opposite the large phenyl group in nitrone intermediate **21**, whereas the isoindoline **3b** precursor to the meso nitroxide is formed by the addition of a Grignard reagent from the face opposite the large magnesium oxide group of the tight ion pair of iminium **19**. The assignment of these structures is confirmed by preparation of several derivatives as well as by X-ray crystallography.

Introduction

The preparation of C_2-symmetrical chiral nitroxides has become a topic of current interest due to the application of optically active nitroxides[1] to a number of fields, including asymmetric oxidation,[2] stereoselective trapping of prochiral carbon radicals,[3] nitroxide mediated "living" free radical polymerization,[4] and paramagnetic chiral liquid crystals.[5] Reduction of these nitroxides provides access to the corresponding C_2-symmetrical chiral secondary amines,[6] which are of interest in asymmetric deprotonation, as optically active ligands, and as chiral auxiliaries. A number of isolable trans C_2-symmetric nitroxides have been prepared in which the asymmetric substituents are either immediately adjacent to the nitrogen on a pyrrolidine[7] or piperidine ring[8] of type **1a**, a pyrrolidine ring of type **1b**,[9] a pyrrolidine[10] or piperidine ring[11] of type **1c**, or are remote to the nitrogen on an azepine **1d**[2b] or pyrrolidine ring **1e**.[12] The technique



traditionally employed for the preparation of C_2-symmetrical chiral nitroxides of types **1a**−**c** was originally developed by Keana[13] and relies on the addition of a Grignard reagent anti to a transannular bulky substitu-

(1) Review on the synthesis and applications of optically active nitroxides: Naik, N.; Braslau, R. *Tetrahedron* **1998**, *54*, 667−696.

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(3) (a) Braslau, R.; Burrill, L. C.; Mahal, L. K.; Wedeking, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 237−238. (b) Braslau, R.; Burrill, L. C.; Chaplinski, V.; Howden, R.; Papa, P. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3209−3212.

(4) (a) Puts, R. S.; Sogah D. Y. *Macromolecules* **1996**, *29*, 3323−3325. (b) Hawker has shown by crossover experiments that the mediating nitroxides undergo facile exchange during these "living" polymerizations; thus, the simple use of an optically active nitroxide is not likely to result in optically active polymers: Hawker, C. J. *Acc. Chem. Res.* **1997**, *30*, 373−382.

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(7) (a) Keana, J. F. W.; Cuomo, J.; Lex, L.; Seyedrezai, S. *J. Org. Chem.* **1983**, *48*, 2647−2654. (b) Hankovszky, H. O.; Hideg, K.; Lovas, M. J.; Jerkovich, G.; Rockenbauer, A.; Györ, M.; Sohár, P. *Can. J. Chem.* **1989**, *67*, 1392−1400. (c) Benfaremo, N.; Steenbock, M.; Klapper, M.; Müllen, K.; Enkelmann, V.; Cabrera, K. *Liebigs Ann. Chem.* **1996**, 1413−1415. (d) Puts and Sogah, ref 4a. (e) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Gautier-Luneau, I.; Pierre, J.-L. *J. Org. Chem.* **1997**, *62*, 9385−9388.

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(9) Rockenbauer, A.; Mercier, A.; LeMoigne, F.; Olive, G.; Tordo, P. *J. Phys. Chem. A* **1997**, *101*, 7965−7970.

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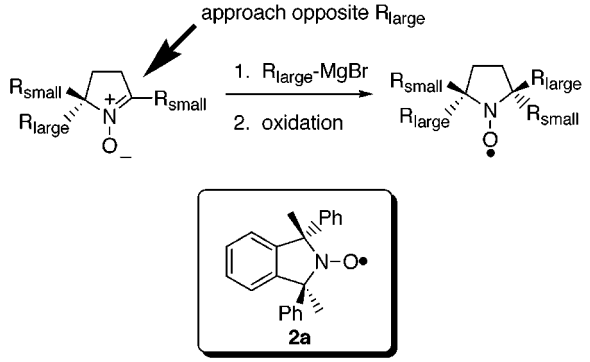
(11) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Chem. Soc., Chem. Commun.* **1995**, 1029−1030.

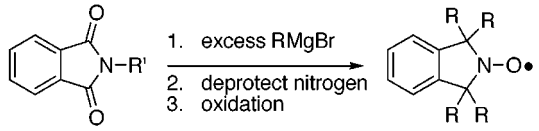
(12) Keana, J. F. W.; Hideg, K.; Birrell, G. B.; Hankovszky, O. H.; Ferguson, G. L.; Parvez, M. *Can. J. Chem.* **1982**, *60*, 1439−1447.

10.1021/jo981614d CCC: $15.00
Published on Web 12/04/1998

Scheme 1



Scheme 2

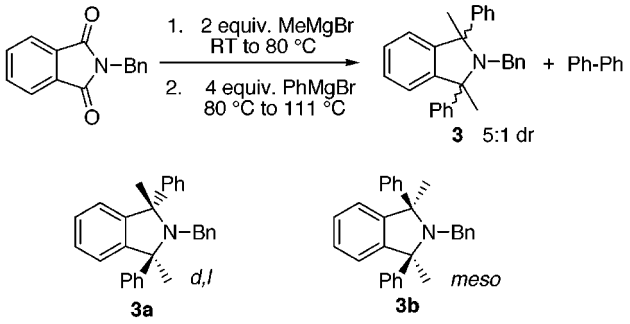


ent in a nitrone intermediate as shown in Scheme 1. This paper describes several approaches to the formation of the isoindole-based C_2-symmetrical nitroxide **2a**,[14] in which the aromatic ring imposes two sp^2 planar carbon atoms on the pyrrolidine nitroxide ring. Historically, isoindoline nitroxides derived from phthalimides have been prepared by the addition of a greater than 4-fold excess of a single Grignard reagent to an *N*-alkyl phthalimide,[15] followed by oxidation (Scheme 2). The approaches outlined herein allow variation in the substitution around the nitroxide.

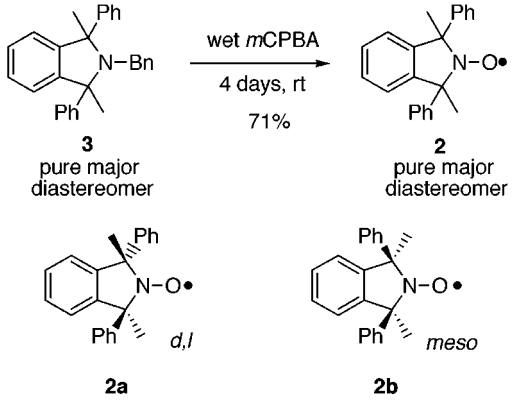
Results and Discussion

N-Benzyl phthalimide was chosen for ease of deprotection of the nitrogen in anticipation of eventual nitroxide formation. Experimentation with stepwise addition of two equiv of methylmagnesium bromide at room temperature followed by heating at 80 °C for 30 min, and then introduction of 4 equiv of phenylmagnesium bromide at 80 °C followed by toluene reflux for 12 h, resulted in a mixture of biphenyl plus a product resulting from net addition of two methyl groups and two phenyl groups (Scheme 3). Purification by flash chromatography provided the product **3** as a 5:1 mixture of diastereomers in 25% yield. The major component was obtained in purified form following two recrystallizations, in 17% overall yield. NMR spectroscopy confirmed that amine **3** was symmetrically substituted, but failed to differentiate between a trans-substituted *d*,*l* product **3a** and a cis-substituted meso product **3b**. Oxidation with wet 50% *m*-CPBA over 4 d provided the corresponding nitroxide in 71% yield, directly, without necessitating a separate step for the removal of the benzyl protecting group.[15a] Benzoic acid is presumed to be the side product formed from the benzyl

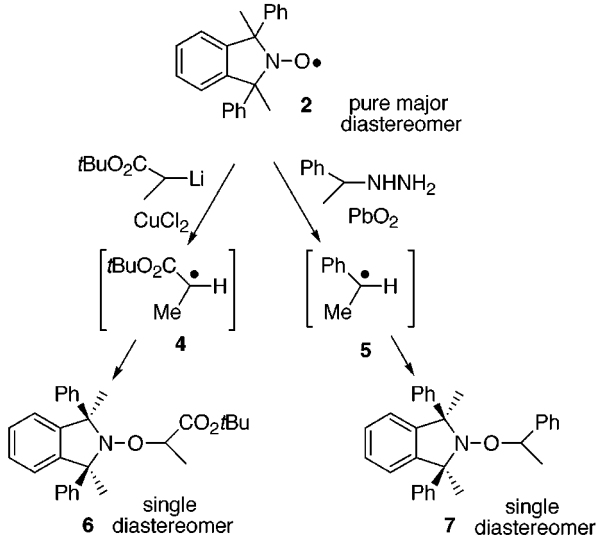
Scheme 3



Scheme 4



Scheme 5



residue. Precedence based on work with nitrone intermediates leads one to expect the formation of the trans-substituted amine **3a** and, thus, formation of *d*,*l* nitroxide **2a** as the major product (Scheme 4).

Coupling of the nitroxide **2** with two different prochiral radicals,[16] **4** and **5**, surprisingly formed the *N*-alkoxy products **6** and **7**, respectively, as single diastereomers (Scheme 5). This could be a result of excellent stereoselectivity in the approach of a C_2-symmetrical nitroxide to the prochiral carbon radicals or the reaction of an achiral *meso*-nitroxide with the carbon radicals. To differentiate between these two possibilities (Scheme 6),

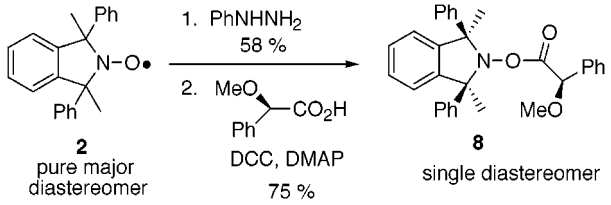
(13) Trans addition is only ensured when the steric bulk of R$_{large}$ is significantly big compared to R$_{small}$ on the nitrone intermediate: Lee, T. D.; Birrell, G. B.; Keana, J. F. W. *J. Am. Chem. Soc.* **1978**, *100*, 1618−1619.

(14) Both the meso and d, l diastereomers of this nitroxide have been generated as a mixture by cheletropic trapping of nitric oxide in an ESR tube: Paul, T.; Hassan, M. A.; Korth, H.-G.; Sustmann, R.; Avila, D. V. *J. Org. Chem.* **1996**, *61*, 6835−6848.

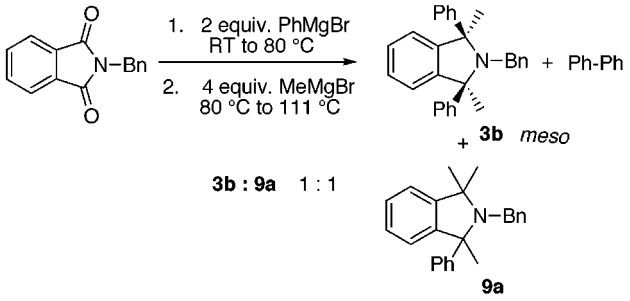
(15) (a) Griffiths, P. G.; Moad, G.; Rizzardo, E.; Solomon, D. H. *Aust. J. Chem.* **1983**, *36*, 397−401. (b) Sholle, V. D.; Krinitskaya, L. A.; Rozantsev, E. G. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1969**, 138.

(16) Braslau, R.; Burrill, L. C.; Siano, M.; Naik, N.; Howden, R. K.; Mahal, L. K. *Macromolecules* **1997**, *30*, 6445−6450.

Scheme 6



Scheme 7

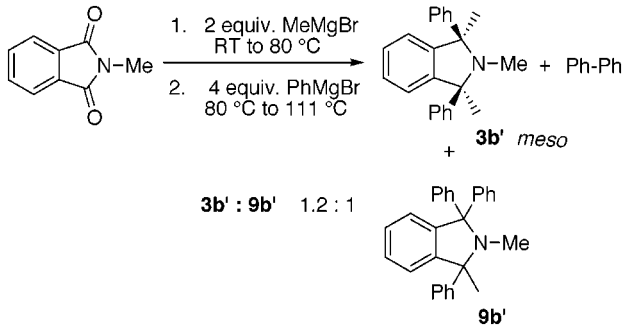


the nitroxide was reduced to the hydroxylamine with phenyl hydrazine, followed by esterification with optically active (*R*)-(−)-α-methoxyphenylacetic acid. Both ^{1}H and ^{13}C NMR spectroscopy indicate formation of a single product, **8**, implying cis substitution of the phenyl groups. Thus, the correct structure for the major Grignard addition product is *meso*-**3b** rather than the expected *d*,*l*-**3a**, and that for the nitroxide is *meso*-**2b** rather than C_2-symmetric **2a**. X-ray crystallography on both the *N*-benzylated amine and the nitroxide confirm the meso structure. The X-ray structure for benzylamine **3b** shows the isoindoline ring to be slightly bent, with the nitrogen atom out of the plane defined by the rest of the isoindoline ring system. The two methyl groups are in axial-like positions, with a bond angle of 109.1° from the aromatic plane. The phenyl groups are situated with a wider angle from the aromatic plane, of 111.9°. For *meso*-nitroxide **2b**, the isoindole ring is completely planar, as is expected for the sp^2 hybridization at the nitroxide nitrogen atom.

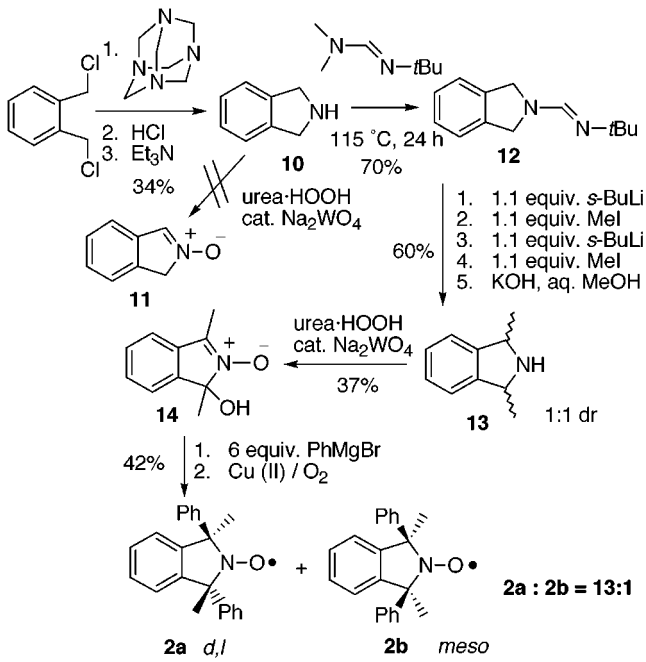
The Grignard addition reaction was then reexamined to determine if the ratio of *d*,*l* versus meso product formation could be controlled by the order of addition of the two Grignard reagents (Scheme 7). Thus, 2 equiv of phenylmagnesium bromide were added to *N*-benzyl phthalimide at room temperature over a 5-min period. A violet precipitate formed and partially redissolved, following the completion of the addition of the first Grignard reagent. The reaction mixture was heated to 80 °C for 30 min, followed by addition of 4 equiv of methylmagnesium bromide. This mixture was then heated at toluene reflux for 12 h. Workup provided the *meso*-dimethyl-substituted amine **3b** in a 1:1 ratio with the trimethyl-substituted amine **9a**. Biphenyl was also produced. Chromatography provided the products **3b** and **9a** in 20 and 23% yield, respectively. Use of *N*-methyl phthalimide as the starting material (Scheme 8) gave 15% of *meso*-**3b′**, the *N*-methyl analogue of **3b**, and 12% of the triphenyl-substituted amine **9b′**. To confirm the cis stereochemistry, oxidative demethylation[17] of *N*-methyl **3b′** to form the nitroxide, followed by reduction with phenyl hydrazine and esterification with optically active (*R*)-(−)-α-methoxyphenylacetic acid, gave the same

(17) Dupeyre, R.-M.; Rassat, A. *Tetrahedron Lett.* **1975**, 1839−1840.

Scheme 8



Scheme 9



product **8** as shown in Scheme 6. These experiments indicate there is an inherent bias for formation of the meso diastereomer by this synthetic route.

Attention was next focused on the traditional nitrone route for C_2-symmetrical chiral-nitroxide formation (Scheme 9). Indoline **10** was prepared using the Delépine reaction[18] according to the procedure by Meyers.[19] Attempts to prepare nitrone **11** using urea−hydrogen peroxide complex with a tungsten catalyst[20] gave an intractable tar. However, stepwise methylation of the formamidine **12**, following the procedures of Rockell[21] and Meyers,[19] provided the dimethyl-substituted amine **13** as an approximately 1:1 mixture of diastereomers in 60% overall yield. Oxidation unexpectedly produced hydroxynitrone **14**. This material was treated with an excess of phenyl Grignard at toluene reflux for 12 h. After an aqueous workup, the crude hydroxylamine was submitted to copper-catalyzed air oxidation to provide the desired *d*,*l*-nitroxide **2a**, as a 13:1 diastereomeric mixture with **2b**, obtained in 42% overall yield from hydroxynitrone

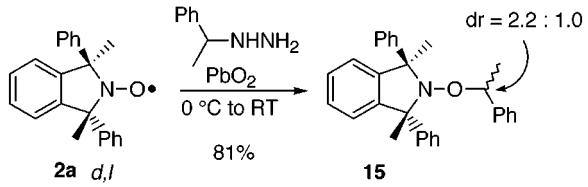
(18) Delépine, M. *Compt. Rend.* **1895**, *120*, 501; **1897**, *124*, 292. Angyal, S. J. *Org. React.* **1954**, *8*, 197.

(19) Meyers, A. I.; Santiago, B. *Tetrahedron Lett.* **1995**, *36*, 5877−5880.

(20) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett.* **1995**, *36*, 3561−3562.

(21) Beeley, L. J.; Rockell, C. J. M. *Tetrahedron Lett.* **1990**, *31*, 417−420.

Scheme 10



14 following purification by flash chromatography. This material was clearly different from the *meso*-**2b**: the melting points for **2a** and **2b** are 139−141 and 105−108 °C, respectively. In addition, *in situ* reduction of nitroxides **2a** and **2b** with phenyl hydrazine in separate NMR tubes give the corresponding hydroxylamines in which the methyl resonances are observed at δ 1.70 and 1.95 ppm. Confirming the chiral nature of **2a**, coupling with the prochiral 1-phenethyl radical provided the alkoxyamine product **15** as a 2.2:1 mixture of diastereomers (Scheme 10). Interestingly, the room-temperature NMR spectra of alkoxyamines **6**, **7**, and **8** derived from *meso*-nitroxide **2b** show no hint of hindered nitrogen inversion coupled with slow N−O-bond rotation,[22] whereas the room-temperature ^{1}H NMR spectrum of **15** derived from *d*,*l*-nitroxide **2a** does show broadened isoindoline methyl peaks from this phenomenon. An X-ray crystal structure of **2a** confirms the C_2 symmetry of the molecule. The isoindoline ring is clearly planar, with the phenyl groups splayed across opposite sides of the fused ring system.

The formation of the meso product from the phthalimide starting material can be understood by considering the following mechanistic route depicted in Scheme 11. Following the addition of the first equivalent of methyl Grignard, the second equivalent adds to the face opposite the large alkoxy magnesium salt to give *meso*-bis(alkoxide) intermediate **16**. Elimination of OMgBr gives iminium salt **17** as a tight ion pair. Addition of the first equivalent of phenyl Grignard occurs from the face opposite both alkoxy-magnesium bromides, to give intermediate **18**. Subsequent elimination forms iminium species **19**, again as a tight-ion pair. The second equivalent of phenyl Grignard then adds opposite the complexed alkoxy−magnesium salt, to give *meso*-**3b**. In contrast, the nitrone route, starting with compound **14**, is expected to react with phenyl Grignard from the face opposite the alkoxy−magnesium salt to initially give intermediate **20**, which undergoes elimination to produce nitrone **21**. Because of the anionic oxygen bonded to nitrogen, **21** does not exist as a tight-ion pair, and thus addition of the second equivalent of phenyl Grignard occurs from the face opposite the phenyl group, to give intermediate **22**, as normally observed in the Keana method. Although this is a rationalization of the experimental results, this does provide a reasonable guide to understanding the observed stereochemistry with iminium vs nitrone intermediates.

We had also considered thermodynamic equilibration through a dibenzylic tertiary carbocation, **23**, as a rationale for the formation of predominately *meso*-isoindoline from the phthalimide route (Scheme 12). MM2 molecular mechanics calculations on the *N*-methyl isoindolines give a 0.4 kcal/mol difference in energy for these two structures, with the meso compound being more stable. As was seen in the X-ray structure of **3b**, the isoindole ring is bent, with the two axial methyl groups occupying an axial-like position. In **3a**, one of the bulky phenyl groups would be required to sit in an axial-like orientation, destabilizing the C_2-symmetrical isomer. However, submission of a 1.6:1 *d*,*l*/meso mixture of **3a**/**3b** to 2 equiv of phenyl Grignard in refluxing toluene for 15 h, to simulate the reaction conditions, resulted in recovered starting material in exactly the same ratio of 1.6:1 *d*,*l*/meso isomers. This conclusively rules out equilibration via an open cation such as **23**.

This work establishes a procedure for the regio- and diastereoselective introduction of differentiated substituents adjacent to the nitrogen of isoindoline nitroxides. Variation of the substituents, for example, introduction of long alkyl chains for lipid solubility, holds potential for application in the preparation of specialized isoindoline spin probes with narrow line widths.

Experimental Section

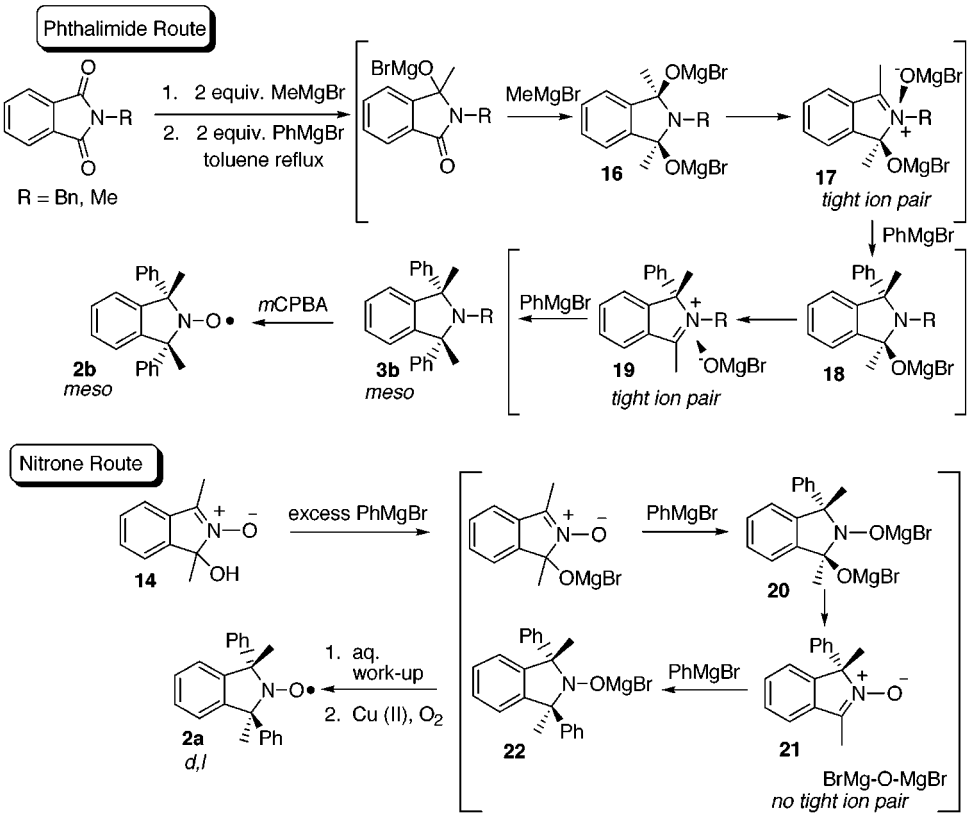
General. All reactions were run under N_2 unless otherwise noted. Phenyl Grignard was purchased from Aldrich and methyl Grignard was purchased from Strem as ether solutions. Solvents were dried as follows: THF and toluene were distilled under N_2 from sodium−benzophenone, and CH_2Cl_2 was distilled from calcium hydride. Flash chromatography was performed using Universal Scientific Inc. silica gel 63-200. IR spectra were recorded in $CDCl_3$ solution. Mass spectra were obtained at the University of Illinois using Magic Bullet or fast-atom bombardment (FAB); electrospray mass spectroscopy (ESMS) was performed at U. C. Santa Cruz using a Quattro II Triplequadrupole mass spectrometer. Elemental Analysis was carried out by M-H-W Laboratories, Phoenix, AZ. The X-ray crystallographic structure was obtained from the facilities at the University of Wyoming. Melting points are uncorrected.

***meso*-2-Benzyl-1,3-dimethyl-1,3-diphenylisoindoline (3b).** *N*-Benzyl phthalimide (1.19 g, 5.0 mmol) was dissolved in 20 mL toluene. A 3.0 M solution of methylmagnesium bromide (3.33 mL, 10.0 mmol) in diethyl ether was added dropwise by cannula at room temperature over 5 min. During the addition, a white precipitate formed and partially redissolved. The temperature was raised to 80 °C for 30 min. A 3.0 M solution of phenylmagnesium bromide (6.66 mL, 20.0 mmol) in diethyl ether was added by cannula over 5 min, and the resulting clear solution was heated to reflux (bath temperature: 120 °C). After 12 h, the reaction mixture was cooled, and 50 mL of concentrated ammonium chloride solution and 50 mL of water were added and stirred until all solids dissolved. To this was added 20 mL of concentrated sodium carbonate solution. The organic layer was separated, washed with 20 mL of brine, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography of the residue (30 mm column, 100:1 hexane/ethyl acetate) was carried out to separate the product from biphenyl, yielding 480 mg of crude product as clear brown solid (25% yield). Two recrystallizations from 3 mL of hexane/ethyl acetate (16:1) gave colorless crystals of **3b**. Alternatively, a single recrystallization from ethanol/chloroform gave very clean crystals. TLC: 100:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.33. Mp: 131 °C. IR ($CDCl_3$): 1214, 1172, 1092 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50−7.38 (m, 4H), 7.30−7.10 (m, 8H), 6.95−6.80 (m, 7H), 3.88 (s, 2H), 1.94 (s, 6H). ^{13}C NMR (APT) (63 MHz, $CDCl_3$): δ 148.5 (s), 148.0 (s), 139.1 (s), 129.0 (d), 127.8 (d), 127.4 (d), 127.2 (d), 127.1 (d), 126.2 (d), 125.9 (d), 122.8 (d), 70.6 (s), 48.0 (t), 23.9 (q). MS (EI): *m*/*e* 374 ([M$^+$ − CH$_3$], 100), 312 ([M$^+$ − Bn], 28), 91 ([Bn$^+$]95). HRMS: exact mass calcd for [M − 15]$^+$ $C_{28}H_{24}N$ 374.1909, found 374.1913.

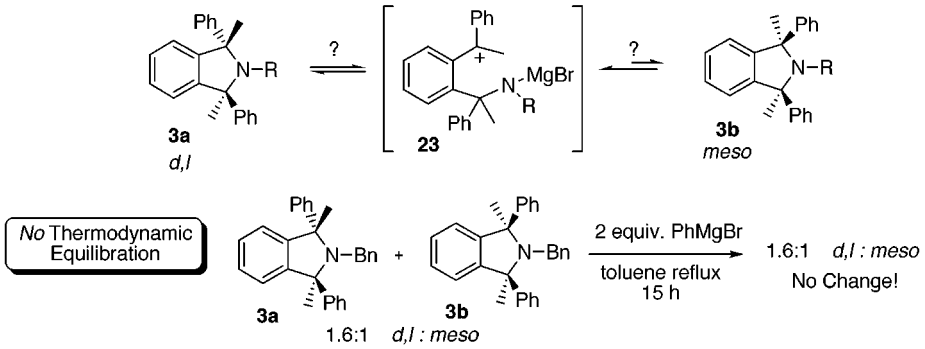
Oxidation of *meso*-2-Benzyl-1,3-dimethyl-1,3-diphenylisoindoline (3b) to the Nitroxide: 1,3-Dimethyl-1,3-diphenylisoindolin-2-yloxyl (2b).[14] Isoindoline **3b** (152 mg, 0.39 mmol) was dissolved in 15 mL of dichloromethane. Wet

(22) Busfield, W. K.; Jenkins, I. D.; Thang, S. H.; Moad, G.; Rizzardo, E.; Solomon, D. H. *J. Chem. Soc., Chem. Commun.* **1985**, 1249−1250.

Scheme 11



Scheme 12



50% *m*-chloroperbenzoic acid (Aldrich) (470 mg, 1.36 mmol) was added with stirring at room temperature under a normal atmosphere. Additional dichloromethane was added over the course of 4 d to dissolve precipitating solids. The reaction was monitored by TLC. After 4 d, the slightly yellow reaction mixture was washed with 35 mL of saturated sodium bicarbonate solution, followed by 5 mL of brine, and dried over magnesium sulfate and the solvent evaporated to provide a yellow oil. Purification by flash column chromatography (10 mm column, 10:1 hexane/ethyl acetate) afforded 87.7 mg of **2b** as a crystalline brown solid (71% yield). Mp: 105−108 °C. TLC: 10:1 hexane/ethyl acetate, molybdenum stain, $R_f = 0.49$. IR ($CDCl_3$): 1366 (N−O•), 1259 (C−N), 1183 (C−N) cm^{-1}. ESR (CH_2Cl_2) triplet, $a_n = 14.22$ G. MS (EI): *m/e* 314 ($[M]^+$, 39). HRMS exact mass calcd for $[M^+]$ $C_{22}H_{20}NO$: 314.1545. Found: 314.1545. ^1H NMR (250 MHz, $CDCl_3$) gave a broad, amorphous spectrum.

Reduction of the 1,3-Dimethyl-1,3-diphenylisoindolin-2-yloxyl (2b) to the Hydroxylamine: 2-Hydroxy-1,3-dimethyl-1,3-diphenylisoindoline. Nitroxide **2b** (51.2 mg, 0.163 mmol) was dissolved in 5 mL of dichloromethane, and phenyl hydrazine (17.6 mg, 0.163 mmol) was added. After 30 min, the almost colorless reaction mixture was concentrated to provide a brown oil. The hydroxylamine was purified by flash column chromatography (10 mm column, 10:1 hexane/ethyl acetate) to afford 29.6 mg of the hydroxylamine as a crystalline colorless solid (58% yield). Mp: 114−117 °C. TLC: 10:1 hexane/ethyl acetate, molybdenum stain, $R_f = 0.51$. ^1H NMR (250 MHz, $CDCl_3$): δ 7.57 (d, 4H, $J = 7.5$ Hz), 7.5−7.1 (m, 8H), 7.05−6.9 (m, 2H), 4.31 (bs, 1H), 1.95 (s, 6H). ^{13}C NMR (APT) (63 MHz, $CDCl_3$): δ 146.99 (s), 145.03 (s), 127.82 (d), 127.37 (d), 127.10 (d), 126.58 (d), 123.09 (d), 72.18 (s), 21.99 (q).

***tert*-Butyl 2-(1,3-Dimethyl-1,3-diphenylisoindolin-2-yloxy)propanoate (6).** Following a modified procedure from Porter,[23] a 2.0 M solution of LDA (135 μL, 0.27 mmol) and 1.0 mL of anhydrous THF were cooled under nitrogen to −78 °C, and a solution of *tert*-butyl propionate (29.3 mg, 0.225 mmol) in 1.0 mL of THF was added dropwise by cannula. The reaction mixture was kept at this temperature for 1.5 h. In a separate flask, anhydrous $CuCl_2$ (36.3 mg, 0.27 mmol) and nitroxide **2b** (47.2 mg, 0.15 mmol) in 1.0 mL of THF were stirred for 5 min and cooled to −78 °C, and the cold enolate solution was

(23) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *28*, 4457−4460.

added by cannula. After 1 h, the reaction was allowed to warm to room temperature. The reaction mixture was concentrated, and the residue was dissolved in the mixture of 5 mL of diethyl ether, 1.0 mL 10% NH_4OH solution, and 2.0 mL of water. The organic layer was separated and washed with 2 mL of saturated sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give crude **6**. Purification by flash column chromatography (10 mm column, 16:1 hexane/ethyl acetate) afforded 47.6 mg of pure **6** as a colorless oil (72% yield) and a single diastereomer.

TLC: 16:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.33. IR ($CDCl_3$): 1731 (C=O), 1449, 1373, 1085 cm^{-1}. ^1H NMR (250 MHz, C_6D_6): δ 8.0−7.7 (m, 4H), 7.4−6.8 (m, 10H), 4.17 (q, 1H, J = 7.0 Hz), 2.38 (s, 3H), 2.11 (s, 3H), 1.31 (s, 9H), 1.16 (d, 3H, J = 7.0 Hz). ^{13}C NMR (APT) (63 MHz, $CDCl_3$): δ 172.19 (s), 147.84 (s), 145.84 (s), 145.11 (s), 127.83 (d), 127.68 (d), 127.53 (d), 127.35 (d), 126.82 (d), 126.52 (d), 123.32 (d), 123.19 (d), 80.86 (d), 80.45 (s), 73.22 (s), 73.03 (s), 27.82 (q), 22.68 (q), 18.12 (q). MS (FAB): *m/e* 444 ([M^+ + 1], (100), 314 ([nitroxide$^+$], 98). HRMS: mass calcd for [M^+ + 1] $C_{29}H_{34}NO_3$ 444.2539, found 444.2539.

1,3-Dimethyl-2-(1-phenylethoxy)-1,3-diphenylisoindoline (7). A two-phase mixture of (1-bromoethyl)benzene (41.1 mg, 0.222 mmol) and fuming hydrazine (0.173 mL, 2.22 mmol) was sonicated for 30 min under nitrogen until a single cloudy phase was observed. The mixture was diluted with 10 mL of diethyl ether, and the organic and hydrazine layers were separated. The hydrazine layer was washed with 5 mL of diethyl ether. The combined organic phase was washed with 5 mL of 10% aqueous potassium hydroxide followed by 5 mL of brine, dried over magnesium sulfate, and filtered. Volatiles were removed in vacuo to give a slightly yellow oil which was diluted with toluene (0.5 mL) and cooled to −78 °C. In a separate flask, lead dioxide (42.5 mg, 0.178 mmol), isoindolinoxyl **2b** (28.0 mg, 0.089 mmol), and toluene (0.5 mL) were sonicated under nitrogen for 5 min and then cooled to −78 °C. The benzylic hydrazine solution was added by cannula, and the residues were washed in with an additional 0.5 mL of toluene. The reaction was allowed to warm to room temperature, diluted with 10 mL of diethyl ether, filtered through Celite, and washed with 15 mL of diethyl ether. Volatiles were removed in vacuo to give an orange oil. Purification by flash column chromatography (10 mm column, 50:1−16:1 hexane/ethyl acetate) afforded 24.2 mg of impure coupling product **7** as an oil and 10.4 mg of the hydroxyamine (28% yield) as a slightly yellow oil. Further purification by flash column chromatography (10 mm column, 5:1 hexane/dichloromethane) afforded 12.0 mg of slightly impure **7** as a colorless oil (32% yield) and a single diastereomer. TLC: 32:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.30. TLC: 5:1 hexane/dichloromethane, molybdenum stain, R_f = 0.34. IR ($CDCl_3$): 3025, 1449, 1301, 1067 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.60 (d, 2H, J = 7.3 Hz), 7.5−6.7 (m, 17H), 4.12 (q, 1H, J = 6.5 Hz), 1.99 (s, 3H), 1.86 (s, 3H), 0.84 (d, 3H, J = 6.5 Hz). ^{13}C NMR (APT) (63 MHz, $CDCl_3$): δ 148.29 (s), 147.99 (s), 146.35 (s), 145.87 (s), 143.68 (d), 128.16 (d), 127.8 (d), 127.73 (d), 127.6 (d), 127.53 (d), 126.92 (d), 126.76 (d), 126.49 (d), 126.37 (d), 123.3 (d), 80.85 (d), 73.11 (s), 72.88 (s), 22.75 (q), 22.59 (q), 21.78 (q). MS (FAB): *m/e* 420 ([M^+ + 1], 18), 315 ([nitroxide$^+$ + 1], 88), 300 ([nitroxide$^+$ − CH_2], 100), 104 ([styrene$^+$], 79). HRMS: mass calcd for [M^+ + 1] $C_{30}H_{30}NO$ 420.23274, found 420.2328.

Acylation of the Hydroxylamine of 2b with (*R*)-(−)-α-Methoxyphenylacetic Acid: 1,3-Dimethyl-1,3-diphenylisoindolin-2-ol α-Methoxyphenylacetate (8). (*R*)-(−)-α-Methoxyphenylacetic acid (15.6 mg, 0.094 mmol), 4-*N*,*N*-(dimethylamino)pyridine (1.2 mg, 0.0094 mmol), and 1,3-dicyclohexylcarbodiimide (58.0 mg, 0.107 mmol) were suspended in 1.5 mL of dichloromethane. A solution of hydroxylamine derived from **2b** (26.8 mg, 0.085 mmol) in 0.5 mL of dichloromethane was added dropwise by cannula. The residues of the hydroxylamine were washed into the reaction mixture with 2 × 0.5 mL of dichloromethane. After 2 h, the heterogeneous mixture was filtered, and the cake of dicyclohexylurea was washed with 3 × 1 mL of hexanes. The filtrate was washed with 0.5 mL of 1 N hydrochloric acid, followed by 2 × 0.5 mL of saturated sodium bicarbonate solution and 2 × 0.5 mL of brine, dried over magnesium sulfate, and concentrated into an oil. The ester was purified by flash column chromatography (10 mm column, 10:1 hexane/ethyl acetate) to afford 29.6 mg of **8** as a colorless oil (75% yield). TLC: 10:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.41. IR ($CDCl_3$): 3060, 1766, 1449, 1096 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.5−6.9 (m, 19H), 4.71 (s, 1H), 3.35 (s, 3H), 1.78 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (APT) (63 MHz, $CDCl_3$) δ 169.19 (s), 144.81 (s), 144.65 (s), 144.45 (s), 135.95 (s), 128.58 (d), 128.31 (d), 127.54 (d), 127.25 (d), 127.10 (d), 127.00 (d), 126.22 (d), 126.16 (d), 123.64 (d), 81.46 (d), 57.14 (q), 25.17 (q), 24.59 (q). MS (FAB): *m/e* 464 ([M^+ + 1], 24), 121 ([PhCH=OMe]$^+$, 100). HRMS: mass calcd for [M^+ + 1] $C_{31}H_{30}NO_3$ 464.2226, found 464.2224.

2-Benzyl-1,3,3-trimethyl-1-phenylisoindoline (9a) as a 1:1 Mixture with *meso*-2-Benzyl-1,3-dimethyl-1,3-diphenylisoindoline (3b). *N*-Benzylphthalimide (1.19 g, 5.0 mmol) was dissolved in 20 mL of toluene. A 3.0 M solution of phenylmagnesium bromide (3.33 mL, 10.0 mmol) in diethyl ether was added dropwise by cannula at room temperature over 5 min. During the addition, a violet precipitate formed, which partially dissolved again at the end of the addition. The mixture was heated at 80 °C for 30 min. A 3.0 M solution of methylmagnesium bromide (6.66 mL, 20.0 mmol) in diethyl ether was added by cannula over 5 min; the resulting yellow solution was heated to reflux (bath temperature 120 °C). After 12 h, the mixture was cooled, and 50 mL of concentrated ammonium chloride solution and 25 mL of water were added to dissolve all solids. To this was added 20 mL of concentrated sodium carbonate solution, and the organic layer was washed with 20 mL of brine, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography of the residue (30 mm column, 100:1 hexane/ethyl acetate) removed biphenyl, giving 64 mg of pure 2-benzyl-1,3,3-trimethyl-1-phenylisoindoline (**9a**) as a colorless oil and a mixture of isoindolines **3b** and **9a**, which was chromatographed again. This gave 522 mg of a clean 1:1 isoindolines mixture and 380 mg of a mixture containing 43% of **3b** and 8% of **9a**, as determined by ^1H NMR analysis. In summary, the combined yields of isoindolines **3b** and **9a** in the reaction were 23 and 20%, respectively.

2-Benzyl-1,3,3-trimethyl-1-phenylisoindoline (9a). TLC: 100:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.31. IR ($CDCl_3$): 3026, 1212, 1027 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.5−6.8 (m, 14H), 3.82 (dd, 2H), 1.77 (s, 3H), 1.46 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (APT) (63 MHz, $CDCl_3$): δ 148.26 (s), 147.81 (s), 147.44 (s), 141.96 (s), 128.89 (d), 128.1 (d), 127.77 (d), 127.52 (d), 127.1 (d), 126.98 (d), 126.43 (d), 122.82 (d), 121.3 (d), 71.18 (s), 65.51 (s), 47.4 (t), 30.07 (q), 27.66 (q), 24.94 (q). MS (EI): *m/e* 327 ([M]$^+$, 4), 313 ([M^+ − 14], 37), 250 ([M^+ − Ph], 15), 91 ([Bn]$^+$, 100). HRMS: mass calcd for [M]$^+$ $C_{24}H_{25}N$ 327.1987, found 327.1986.

***meso*-1,2,3-Trimethyl-1,3-diphenylisoindoline (3b′) and 1,2-Dimethyl-1,3,3-triphenylisoindoline (9b′).** The *N*-methylphthalimide (806 mg, 5.0 mmol) was dissolved in 20 mL of toluene. A 3.0 M solution of methylmagnesium bromide (3.33 mL, 10.0 mmol) in diethyl ether was added dropwise by cannula at room temperature over 5 min. During the addition, a white precipitate formed. The mixture was heated at 80 °C for 30 min. A 3.0 M solution of phenylmagnesium bromide (6.66 mL, 20.0 mmol) in diethyl ether was added by cannula over 5 min, and the resulting clear solution was heated to reflux (bath temperature 120 °C), becoming yellow and almost clear after 1 h. After 20 h, the reaction mixture was cooled, and 25 mL of concentrated ammonium chloride solution and 25 mL of water were added until most of the solids dissolved. A dark emulsion formed which was filtered through sintered glass and washed with 20 mL of hexanes. The organic layer was separated, washed with 20 mL of brine, dried over magnesium sulfate, and concentrated in vacuo. Four flash chromatography columns were required to obtain analytical samples of isoindolines **3b′** and **9b′**, in overall yields of 15 and 12%, respectively.

1,2,3-Trimethyl-1,3-diphenylisoindoline (3b′). TLC: 40:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.35. IR

($CDCl_3$): 1224, 1066, 1026 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.7−6.9 (m, 14H), 2.25 (s, 3H), 1.87 (s, 6H). ^{13}C NMR (APT) (63 MHz, $CDCl_3$): δ 147.9 (s), 147.5 (s), 128.0 (d), 127.7 (d), 127.1 (d), 126.6 (d), 122.8 (d), 70.0 (s), 26.6 (q), 23.5 (q). MS (FAB): *m/e* 314 ([M^+ + 1], 27), 298 ([M^+ − CH_3], 100), 236 ([M^+ − Ph], 26). HRMS: mass calcd for [M^+ + 1] $C_{23}H_{24}N$ 314.1909, found 314.1908.

1,2-Dimethyl-1,3,3-triphenylisoindoline (9b′). TLC: 40:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.38. IR ($CDCl_3$): 3060, 1216, 1028 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.7−6.8 (m, 19H), 2.14 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (APT): (63 MHz, $CDCl_3$): δ 148.9 (s), 147.8 (s), 146.3 (s), 144.7 (s), 143.9 (s), 130.2 (d), 128.3 (d), 128.0 (d), 127.9 (d), 127.6 (d), 127.2 (d), 127.1 (d), 126.9 (d), 126.7 (d), 124.6 (d), 123.0 (d), 78.3 (s), 70.4 (s), 28.8 (q), 21.3 (q). MS (FAB): *m/e* 376 ([M^+ + 1], 18), 360 ([M^+ − CH_3], 61), 298 ([M^+ − Ph], 100). HRMS: exact mass calcd for [M^+ + 1] $C_{28}H_{26}N$ 376.2066, found 376.2058.

Oxidative Demethylation of the 1,2,3-Trimethyl-1,3-diphenylisoindoline (3b′) to the Nitroxide and the Amine: *meso*-1,3-Dimethyl-1,3-diphenylisoindoline 2-Nitroxide (2b) and 1,3-Dimethyl-1,3-diphenylisoindoline. To 1,2,3-trimethyl-1,3-diphenylisoindoline **3b′** (92 mg, 0.27 mmol) and $Na_2WO_4 \cdot 2H_2O$ (4.4 mg, 0.013 mmol) was added 3 mL of methanol followed by 30% aqueous H_2O_2 (135 μL, 1.19 mmol), to give a turbid heterogeneous mixture. After 24 h, 5 mL of methanol and 10 drops of 30% aqueous H_2O_2 were added to the yellow solution. After 12 h, the mixture was concentrated under reduced pressure, dissolved in 10 mL of dichloromethane, washed with 5 mL of water, dried over magnesium sulfate, and filtered, and the solvent was evaporated to provide a yellow oil. Two flash chromatography columns were required to separate the products: (dichloromethane, then 10:1 dichloromethane/ethyl acetate). This afforded 15 mg of nitroxide **2b** as a crystalline brown solid (18% yield) and 22 mg of the secondary amine as a colorless oil (28% yield).

1,3-Dimethyl-1,3-diphenylisoindoline. TLC: pure ethyl acetate, molybdenum stain, R_f = 0.16. IR ($CDCl_3$): 1214, 1172, 1092 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.7−6.9 (m, 14H), 2.45 (br s, 1H), 1.88 (s, 6H).

1-Hydroxy-1,3-dimethyl-1*H*-isoindole 1-oxide (14). A mixture of 1,3-dimethyl-1*H*-isoindoline **13** (420 mg, 2.80 mmol, mixture of diastereomers) and $Na_2WO_4 \cdot 2H_2O$ (46 mg, 0.14 mmol) was suspended in 5 mL of methanol and cooled to 0 °C. Urea−hydrogen peroxide addition complex (530 mg, 5.6 mmol) was added. After 1 h of stirring, more urea−hydrogen peroxide addition complex (530 mg, 5.6 mmol) was added. After 2 h, the mixture was concentrated under reduced pressure. Twice the residue was triturated with 20 mL of dichloromethane and filtered to remove the urea. The solvent was evaporated to provide a pale yellow oil which was purified by flash column chromatography (30 mm column, 5:1 ethyl acetate/methanol) to give 170 mg (37% yield) of **14** as a crystalline brown solid; dec 125−130 °C. TLC: 5:1 ethyl acetate/methanol, molybdenum stain, R_f = 0.47. IR ($CDCl_3$): 3072 (broad), 1567 (C=N), 1220 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.61 (br s, 1H), 7.5−7.2 (m, 4H), 2.35 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (APT) (63 MHz, $CDCl_3$): δ 141.6 (s), 141.3 (s), 133.3 (s), 129.6 (d), 129.1 (d), 122.1 (d), 119.8 (d), 77.1 (s), 24.5 (q), 9.5 (q). ESMS: *m/e* 178.10.

***d,l*-1,3-Dimethyl-1,3-diphenylisoindoline 2-Nitroxide (2a).**[14] 1-Hydroxy-1,3-dimethyl-1*H*-isoindole 1-oxide (**14**) (88 mg, 0.5 mmol) was suspended in 3 mL of toluene and heated to 60 °C. To this was added phenylmagnesium bromide, as a 3.0 M solution in diethyl ether (1.00 mL, 3.0 mmol), dropwise by cannula over 1 min. A small amount of white precipitate formed, which quickly redissolved. The clear solution was heated to reflux (bath temperature 120 °C) for 12 h. The resulting dark-red mixture was cooled, and 10 mL of concentrated ammonium chloride solution, 5 mL of water, and 10 mL of diethyl ether were added to get all solids to dissolve. The organic layer was separated, and the aqueous layer was extracted with 5 mL of diethyl ether. The combined organic layers were concentrated, and the residue was treated with a mixture of 5 mL of methanol, 0.5 mL of concentrated NH_4OH, and 5.0 mg (0.025 mmol) of $Cu(OAc)_2$ to give a pink-red solution. A stream of air was bubbled through the solution for 30 min. The resulting green solution was concentrated, and the residue dissolved in the mixture of 10 mL of chloroform, 3 mL of concentrated $NaHSO_4$ solution, and 10 mL of water. The organic layer was separated, and the aqueous layer was extracted with 5 mL of chloroform. The combined organic layers were then washed with 5 mL of saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated in vacuo to give crude nitroxide **2a**. Purification by flash column chromatography (10 mm column, 10:1 hexane/ethyl acetate) afforded 66 mg of 13:1 **2a/2b** as a pale brown solid (42% yield). mp: 139−141 °C. TLC: 16:1 hexane/ethyl acetate, molybdenum stain, R_f = 0.41. IR ($CDCl_3$) 3063, 1369 (N−O•), 1259 (C−N), 1190 (C−N) cm^{-1}. ESR (CH_2Cl_2): triplet, a_n = 14.663 G. MS (FAB): *m/e* 316 ([M^+ + 2], 94), 300 (100). HRMS: mass calcd for [M^+ + 2] $C_{22}H_{22}NO$ 316.1701, found 316.1701. ^1H NMR (250 MHz, $CDCl_3$) gave a broad, amorphous spectrum. Addition of phenyl hydrazine formed the corresponding hydroxylamine: δ 1.70 (s, 6H).

Coupling of *d,l*-1,3-Dimethyl-1,3-diphenylisoindoline 2-Nitroxide (2a) with 1-Phenethyl Radical: 1,3-Dimethyl-2-(1-phenylethoxy)-1,3-diphenylisoindoline (15). A two-phase mixture of (1-bromoethyl)benzene (46.3 mg, 0.250 mmol) and fuming hydrazine (0.78 mL, 2.50 mmol) was sonicated for 30 min under nitrogen until a single cloudy phase was observed. The mixture was diluted with 5 mL of 10% aqueous potassium hydroxide followed by 5 mL of diethyl ether. The water−hydrazine layer was washed with 5 mL of diethyl ether. The combined organic phase was washed with 5 mL of 10% aqueous potassium hydroxide followed by 5 mL of brine, dried over magnesium sulfate, and filtered. Volatiles were removed in vacuo to give a slightly yellow oil which was diluted with toluene (0.5 mL) and cooled to 0 °C. In a separate flask, lead dioxide (72.0 mg, 0.300 mmol), *d,l*-isoindoline nitroxide **2a** (31.4 mg, 0.100 mmol), and toluene (0.5 mL) were sonicated under nitrogen for 5 min and then cooled to 0 °C. The benzylic hydrazine solution was added by cannula, and the residues were washed in with an additional 0.5 mL of toluene. After 5 min, the ice bath was removed, and the reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was diluted with 5 mL of diethyl ether and filtered through Celite, the Celite was washed with 7 mL of diethyl ether, and volatiles were removed in vacuo to give a pale-yellow oil. Purification by flash column chromatography (10 mm column, 5:1 hexane/dichloromethane) afforded 34.0 mg of pure coupling product **15** as a colorless oil (81% yield) and an inseparable 2.2:1 mixture of diastereomers (as indicated by integration of the methyl hydrogens at δ 2.16 and 1.73 ppm). TLC: 5:1 hexane/dichloromethane, molybdenum stain, R_f = 0.28. IR ($CDCl_3$): 3061, 1448, 1370, 1070 cm^{-1}. ^1H NMR (500 MHz, C_6D_6, both diastereomers): δ 7.8−6.6 (m, 19H), 4.51−4.44 (q + q, 1H, both diastereomers), 2.16 (s, 3H, minor diastereomer), 1.73 (s, 3H, major diastereomer), 1.62 (s, 3H, major diastereomer), 1.57 (s, 3H, minor diastereomer), 1.54 (d, 3H, J = 6.5 Hz, minor diastereomer), 1.12 (d, 3H, J = 7.0 Hz, major diastereomer). ^{13}C NMR (APT) (63 MHz, $CDCl_3$, both diastereomers): δ 148.7 (s), 147.6 (s), 144.0 (s), 143.6 (s), 143.2 (s), 129.9 (d), 129.7 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.73 (d), 127.65 (d), 127.5 (d), 127.4 (d), 127.0 (d), 126.9 (d), 126.82 (d), 126.76 (d), 126.5 (d), 126.3 (d), 123.5 (d), 123.3 (d), 121.6 (d), 81.7 (d), 80.4 (d), 72.5 (s), 72.2 (s), 29.1 (q), 28.3 (q), 22.7 (q), 22.5 (q), 21.1 (q), 20.1 (q). MS (FAB): *m/e* 420 ([M^+ + 1], 15), 315 ([nitroxide$^+$ + 1], 100), 300 ([nitroxide$^+$ − CH_2], 77), 104 ([styrene]$^+$, 63). HRMS: mass calcd for [M^+ + 1] $C_{30}H_{30}NO$ 420.2327, found 420.2328.

Acknowledgment. We thank the National Science Foundation (CHE-9527647) for financial support, Professor Glenn Millhauser for the ESR spectrum, Marc Anderson for molecular mechanics calculations, and Dr. Steven Bottle for constructive discussion. Electrospray

mass spectra were taken on a MICROMASS Quattro II Triplequadrupole instrument, the purchase of which was made possible by a generous gift from the W.M. Keck Foundation.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds. For compounds **2a**, **2b** and **3b**, details of the X-ray crystal structure data acquisition and thermal ellipsoid plot of the structure (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981614D