Low-Temperature Preparations of Unimolecular Nitroxide Initiators for "Living" Free Radical Polymerizations

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ABSTRACT: Low-temperature methods for the preparation of monomeric initiators for use in "living" free radical olefin polymerizations have been developed. Oxidative methods for generating carbon radicals in the presence of nitroxide traps such as TEMPO utilize PbO_2 with benzylic, alkyl, or phenylhydrazines or $CuCl_2$ with lithium enolates. Photolytic methods employ $[Cp(CO)_2Fe]_2$ with a benzylic bromide, diphenyl disulfide with styrene, or di-*tert*-butyl peroxide with ethers. The use of di-*tert*-butyl hyponitrite with ethers generates carbon radicals at 50 °C that are trapped by TEMPO.

Introduction

The development of nitroxide-mediated "living" free radical polymerization of olefins provides a method of controlling the polydispersity and molecular weight of growing polymer chains.[1] This enhanced control is a direct consequence of a very fast coupling reaction of nitroxide radicals such as TEMPO with polymer chain-end radicals,[2] a slow, thermally driven fragmentation of the temporarily capped "living" polymer to regenerate the nitroxide and the polymer radical, and the hesitancy of the nitroxide to add to the olefin monomer to initiate new chains.[3] Recently, Hawker[4] has demonstrated that unimolecular initiators[5] consisting of the nitroxide coupled to a benzylic carbon species afford better control over polydispersity and molecular weight than the more commonly utilized bimolecular systems consisting of a traditional free radical initiator such as BPO or AIBN used in conjunction with the free nitroxide.

In work directed toward controlling the stereochemistry of radical reactions, we have been probing the ability of chiral nitroxides to distinguish between the enantiotopic faces of prochiral radicals in coupling reactions at low temperatures.[6] While developing methodologies for generating stoichiometric carbon radicals for these nitroxide trapping studies, we have prepared a number of nitroxide-coupled monomers under a variety of mild reaction conditions. In all cases the coupling reactions are carried out well below the temperatures at which the nitroxide initiator thermally fragments. Herein we describe procedures based on oxidation of alkylhydrazines, oxidation of enolates, photolytic reaction of a benzyl bromide with an organoiron reagent, photolytic thiyl radical addition to styrene, and alkoxy radical hydrogen abstractions to generate carbon radicals in the presence of nitroxide traps. These methodologies should be useful in the preparation of a variety of unimolecular initiators and provide access to initiators with functionalities not available by the alternative methods.[7]

Experimental Section

All reactions were run under nitrogen. Reactions involving the coupling of TEMPO with transient carbon radicals generated *in situ* were purged of oxygen by bubbling nitrogen through the reaction solvent for at least 15 min prior to use. Toluene, benzene, tetrahydrofuran, and diethyl ether were distilled from sodium/benzophenone. Dichloromethane was distilled from CaH_2. $CuCl_2$ was dried at 100 °C under house vacuum overnight before use. Flash chromatography was performed using Universal Scientific Inc. silica gel 63-200. IR spectra were recorded in $CDCl_3$ solution on a Perkin-Elmer 1600 FTIR spectrometer. NMR spectra were recorded on a Bruker ACF dual probe 250-MHz or a Varian 500 MHz machine with tetramethylsilane as an internal standard for proton and the $CDCl_3$ triplet as an internal standard for carbon. Mass spectra were obtained using FAB, CI, or EI on a Finnegan 4000 mass spectrometer with the Super Incos Data System or on a VG ZAB-SE reverse geometry spectrometer with a VG 11/250 data system at the University of Illinois. Elemental analysis was carried out by M-H-W Laboratories in Phoenix, AZ. Melting points are uncorrected.

Typical Procedure for the Oxidation of Alkylhydrazines with Lead Dioxide in the Presence of a Nitroxide Radical: Coupling of 1-Phenethyl Radical with TEMPO To Prepare 1-(2,2,6,6-Tetramethylpiperidinyloxy)-1-phenylethane (1). *Note: fuming anhydrous hydrazine is a biohazard and should only be used in a fumehood wearing gloves and safety glasses.* A two-phase mixture of (1-bromoethyl)benzene (0.1967 g, 1.063 mmol) and fuming hydrazine (0.68 mL, 21.26 mmol) was sonicated for 30 min under nitrogen until a single cloudy phase was observed. The mixture was diluted with 20 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 8 mL of 10% aqueous potassium hydroxide followed by 8 mL of saturated aqueous sodium chloride. The organic phase was then 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 (0.0798 g, 0.333 mmol), TEMPO (0.0350 g, 0.244 mmol), and toluene (0.5 mL) were sonicated under nitrogen for 5 min. The benzylic hydrazine solution was added by cannula, and the residues were washed with toluene to give a 0.15 M solution with respect to TEMPO. The reaction was allowed to warm to room temperature, diluted with 11 mL of diethyl ether, filtered through Celite and washed with diethyl ether. Volatiles were removed *in vacuo* to give 0.0885 g of an orange oil. Purification by flash column chromatography (1.5 cm column, 98:2 hexane−ethyl acetate) afforded 0.0458 g of pure product as an oil (78.2% yield) and an additional 0.0159 g of impure product (7.2% yield). TLC: 98:2 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, $R_f = 0.39$. IR ($CDCl_3$): 3063, 2932, 1454, 1364, 1064 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.23−7.33 (m, 5H), 4.78 (q, 1H, J = 6.7 Hz), 1.49 (d, 3H, J = 6.7 Hz), 1.25−1.50 (m, 6H), 1.30 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H), 0.66 (s, 3H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 145.9 (s), 128.0 (d), 126.8 (d), 126.6 (d), 83.2 (d), 59.7 (s), 40.4 (t), 34.5 (q), 34.2

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(q), 23.6 (q), 20.4 (q), 17.3 (t). Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41. Found: C, 77.98; H, 10.22.

Preparation of 1,2,3,4-tetrahydro-1-naphthyl Bromide. Following the procedure of Schmidt and Brooks,[8] a solution of 1,2-bis(triphenylphosphino)ethane (0.8716 g, 2.19 mmol) dissolved in 11 mL of anhydrous dichloromethane was placed in an ice/salt bath under nitrogen and a solution of bromine (0.2 mL, 4.88 mmol) in 1.2 mL of dichloromethane was added by cannula. Residues of the bromine were washed in with another 1.2 mL of dichloromethane. After 15 min, a solution of 1,2,3,4-tetrahydro-1-naphthol (0.5399 g, 3.64 mmol) in 2.4 mL of dichloromethane was added by cannula. Residues were washed into the reaction flask with another 2.2 mL dichloromethane. After 3 h, the reaction mixture was removed from the ice bath and allowed to stir for 3 h at room temperature. Diethyl ether (36 mL) and pentane (72 mL) were added to form a precipitate, which was removed by filtration through Celite and washed with 2 × 25 mL of 2:1 pentane−diethyl ether. The volatiles were removed *in vacuo* to give 0.6997 g (3.31 mmol, 91% yield) of the product as an orange oil. TLC: 3:2 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, $R_f = 0.89$. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.11−7.43 (m, 4H), 5.66 (m, 1H), 2.90−2.99 (m, 2H), 2.24−2.49 (m, 3H), 1.94−2.00 (m, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 137.00, 136.44, 130.88, 129.50, 128.41, 126.26, 52.21, 33.56, 28.79, 18.91.

Coupling of Tetralinyl Radical with TEMPO To Give 1-(2,2,6,6-Tetramethylpiperidinyloxy)-1,2,3,4-tetrahydro-1-naphthalene (2). The same hydrazine, lead dioxide procedure used to prepare **1** was followed, utilizing 65.4 mg (0.42 mmol) of TEMPO to give 0.2174 g of a yellow oil. Purification by flash column chromatography (30 mm column, 97:3 hexane−ethyl acetate as the solvent) afforded 26.4 mg (22% yield) of the pure product as a cloudy white oil and another 115.9 mg of impure product as a cloudy yellow oil. TLC: 97:3 hexane−ethyl acetate, UV, *p*-anisaldehyde, $R_f = 0.48$; IR ($CDCl_3$): 2973, 1453, 1360, 1063 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.09−7.67 (m, 4H), 4.89−4.91 (m, 1H), 2.77−2.82 (m, 2H), 1.98−2.09 (m, 2H), 1.39−1.58 (m, 8H), 1.27 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 0.75 (s, 3H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 137.84 (quaternary), 137.78 (quaternary), 129.87 (CH), 128.60 (CH), 127.22 (CH), 124.92 (CH), 76.37 (CH), 60.28 (quaternary), 59.97 (quaternary), 40.48 (CH_2), 34.76 (CH_3), 33.38 (CH_3), 29.30 (CH_2), 29.14 (CH_2), 20.95 (CH_3), 20.61 (CH_3), 19.30 (CH_2), 17.39 (CH_2). Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.22; H, 9.96; N, 4.71.

Coupling of 1-(9-Anthranyl)-2,2,2-trifluoroethyl Radical with TEMPO To Prepare 2-(9-Anthranyl)-2-(2,2,6,6-tetramethylpiperidinyloxy)-1,1,1-trifluoroethane (3). A hydrazine, lead dioxide procedure similar to that used to prepare **1** was followed, except that the hydrazine step required addition of chloroform as a cosolvent, and sonication was carried out overnight: 0.145 g of 1-(9-anthranyl)-1-bromo-2,2,2-trifluoroethane, 0.30 mL of neat fuming hydrazine, and 0.20 mL of $CHCl_3$ were sonicated overnight. The rest of the procedure was as described above for **1**, utilizing 63.0 mg (0.40 mmol) of TEMPO. Purification by flash chromatography (98:2 hexane−ethyl acetate, then 4:1 hexane−ethyl acetate) afforded 0.038 g of the product as a yellowish solid containing slight impurities (23% yield), mp 135−140 °C. TLC: 98:2 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, $R_f = 0.10$. IR ($CDCl_3$): 3154.7, 2938.5, 1470.4, 1381.0 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 8.83−8.79 (m, 1H), 8.51 (s, 1H), 8.17−8.13 (m, 1H), 8.05−8.00 (m, 2H), 7.60−7.45 (m, 4H), 6.73 (q, 1H, $J_{HF} = 7.9$ Hz), 1.75−1.20 (m, 6H), 1.57 (s, 3H), 1.38 (s, 3H), 0.76 (s, 3H), 0.44 (s, 3H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 131.8 (s), 130.9 (s), 130.7 (s), 130.5 (s), 129.6 (d), 129.3 (d), 128.7 (d), 126.8 (d), 125.6 (d), 125.0 (d), 124.6 (d), 123.0 (d), 83.8 [(d by APT), q, $J_{CF} = 15.5$ Hz], 61.2 (s), 60.7 (s), 40.8 (t), 40.5 (t), 33.5 (q), 33.4 (q), 21.2 (q), 20.3 (q), 16.9 (t). MS (FAB), *m*/*z*: 416 (4.6), 276 (9.3), 275 (20.4), 260 (20.2), 259 (100), 156 (84.9), 140 (16.8). HRMS exact mass calculated for $[M + 1]^+$ $C_{25}H_{29}NOF_3$ 416.2201, found 416.2204.

Coupling of Phenyl Radical with TEMPO To Prepare 1-(2,2,6,6-Tetramethylpiperidinyloxy)benzene (4). TEMPO (0.1020 g, 0.653 mmol), deoxygenated benzene (4.3 mL), and lead dioxide (0.320 g, 1.34 mmol) were mixed together at room temperature, and phenylhydrazine (128 μL, 1.30 mmol) was added. Gas was immediately evolved. After 10 min, TLC indicated complete consumption of TEMPO. After 40 min total reaction time, the mixture was filtered through Celite and washed with hexanes. Volatiles were removed *in vacuo* to give 0.0777 g of an orange oil, which was purified using silica gel chromatography (1 cm column, hexanes−EtOAc gradient, 5 mL fractions) to give 24.5 mg of the product as a cloudy oil (16% yield). TLC: hexanes, UV, *p*-anisaldehyde stain, $R_f = 0.49$; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.65−7.15 (m, 5H), 1.62−1.40 (m, 6H), 1.24 (s, 6H), 1.02 (s, 6H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 163.7 (s), 128.8 (d), 127.3 (d), 114.0 (d), 60.4 (s), 39.9 (t), 32.7 (q), 20.6 (q), 17.2 (t).

Coupling of 1-Phenethyl Radical with the Doxyl Radical To Prepare 3,3-Dimethyl-*N*-(1-phenylethoxy)-1-oxa-4-azaspiro[4.5]decane (5). The same hydrazine, lead dioxide procedure used to prepare **1** was followed, utilizing 1.015 g (5.51 mmol) of 3,3-dimethyl-*N*-oxyl-1-oxa-4-azaspiro-[4.5]decane[9] to give a bright reddish-orange oil. Purification by flash column chromatography (16:1 hexane−ethyl acetate) provided 0.952 g of a white solid (60% yield). Recrystallization from methanol provided an analytical sample: mp 60−63 °C. The NMR spectra showed two sets of diastereomers due to slow inversion of the nitrogen lone pair on the NMR time scale.[10] TLC: 16:1 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, $R_f = 0.52$. IR ($CDCl_3$): 3036, 2931, 2247, 1598, 1486, 1446, 1262, 1210, 1059, 927, 894, 697 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.32−7.34 (m, 5H), 4.61 (q, 1H, $J = 6.6$ Hz), 3.4−3.6 (m, 2H), 1.0−2.0 (m, 6H), 1.48 (d, 3H, $J = 6.6$ Hz), 1.28 (s, 1.5H), 1.26 (s, 1.5H), 1.07 (s, 1.5H), 0.71 (s, 1.5H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 143.8 (quaternary), 128.6 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 99.5 (quaternary), 99.0 (quaternary), 82.1 (CH), 74.2 (CH_2), 73.7 (CH_2), 63.8 (quaternary), 63.4 (quaternary), 38.0 (CH_2), 37.3 (CH_2), 32.8 (CH_2), 32.7 (CH_2), 27.2 (CH_3), 27.0 (CH_3), 25.7 (CH_2), 25.4 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 23.2 (CH_2), 23.1 (CH_2), 21.9 (CH_3), 21.4 (CH_3). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.7; H, 9.4; N, 4.8. Found: C, 74.56; H, 9.28; N, 4.75.

Coupling of 1-Phenyl-2-propyl Radical with TEMPO To Prepare 1-Phenyl-2-(2,2,6,6-tetramethylpiperidinyloxy)propane (6). A hydrazine, lead dioxide procedure similar to that used to prepare **1** was followed, utilizing 95.5 mg (0.611 mmol) of TEMPO and 350 μL (2.27 mmol) of 1-phenyl-2-bromopropane. Purification by flash chromatography (95:5 hexane−ethyl acetate) afforded 0.0514 g of the product as a yellow oil (30.5% yield). TLC: 95:5 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, $R_f = 0.84$. IR ($CDCl_3$): 2931, 1455, 1376, 1133, 1081 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37−7.20 (m, 5H), 4.14 (dqd, 1H, $J = 8.0$, 6.7, 5.5 Hz), 3.18 (dd, 1H, $J = 13.0$, 5.5 Hz), 2.57 (dd, 1H, $J = 13.0$, 8.0 Hz), 1.53−1.28 (m, 6H), 1.20−1.07 (br m, 12H), 1.14 (d, 3H, $J = 6.7$ Hz). ^{13}C-NMR (APT) (125 MHz, $CDCl_3$): δ 139.9 (s), 129.7 (d), 128.2 (d), 125.9 (d), 79.7 (d), 60.1 (s), 59.5 (s), 43.0 (t), 40.5 (t), 34.7 (q), 34.5 (q), 20.6 (q), 20.5 (q), 19.6 (q), 17.5 (t). MS (CI), *m*/*z*: 275 (1), 157 (21), 142 (100), 119 (16), 91 (66). HRMS exact mass calculated for $[M]^+$ $C_{18}H_{29}NO$ 275.2249, found 275.2245.

Coupling of *tert*-Butyl 2-Propionate Radical with TEMPO To Prepare *tert*-Butyl 2-(2,2,6,6-Tetramethylpiperidinyloxy)propionate (7). Following a modified procedure from Porter,[11] *tert*-butyl propionate (0.15 mL, 0.99 mmol) in 3.2 mL of anhydrous THF was cooled to −78 °C, and 1.15 mL of 1 M LDA was added. In a separate flask, anhydrous $CuCl_2$ (0.138 g, 1.03 mmol) and TEMPO (0.10 g, 0.64 mmol) in 2.0 mL of THF were cooled to −78 °C and added by cannula to the enolate solution. After warming to room temperature overnight, the mixture was filtered through Celite with diethyl ether, then filtered through silica gel, and washed with diethyl ether. The filtrate was washed sequentially with 3.0 mL of water, 3.0 mL of saturated aqueous $NaHSO_4$, and 3.0 mL of brine. After drying over $MgSO_4$, the crude product was purified by flash column chromatography (97:3 hexane−ethyl acetate) to give 0.0959 g of a clear oil (52% yield). TLC: 97:3 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, $R_f = 0.23$; IR ($CDCl_3$): 2978.0, 1736.0, 1448.0 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 4.17 (q, 1H, $J = 7$ Hz), 1.49−1.38 (m, 6H),

1.43 (s, 9H), 1.35 (d, 3H, J = 7 Hz), 1.14 (s, 3H), 1.12 (s, 3H), 1.09 (s, 6H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 173.6 (s), 82.0 (d), 80.5 (s), 61.0 (s), 60 (s), 40.1 (t), 33.6 (q), 33.1 (q), 27.8 (q), 20.0 (q), 18.4 (q), 17.0 (t). MS (EI), m/z: 285 (12), 229 (14), 156 (100), 142 (35), 140 (78), 126 (82). HRMS exact mass calculated for $[M]^+$ $C_{16}H_{31}NO$ 285.2304, found 285.2301.

Coupling of Methyl 2-Isobutyrate Radical with TEMPO To Prepare Methyl 2-Methyl-2-(2,2,6,6-tetramethylpiperidinyloxy)propionate (8). An LDA and $CuCl_2$ procedure similar to that used to prepare **7** was followed, utilizing 0.17 mL (1.500 mmol) of methyl isobutyrate and 156.3 mg (1.000 mmol) of TEMPO. The crude product following aqueous workup (135.6 mg) was clean by both ^{1}H and ^{13}C-NMR spectroscopy; however, impurities were visible by TLC. Filtration through a plug of silica gel in 9:1 hexanes−EtOAc provided 117.9 mg of the product (46% yield) as a clear oil. TLC: 4:1 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.62. IR ($CDCl_3$): 2975, 1724, 1471 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 3.68 (s, 3H), 1.47−1.23 (m, 6H), 1.45 (s, 6H), 1.12 (s, 6H), 0.97 (s, 6H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 176.6 (s), 81.0 (s), 59.4 (s), 51.9 (q), 40.5 (t), 33.3 (q), 24.4 (q), 20.4 (q), 17.0 (t). MS (EI), m/z: 257 (0.9), 242 (0.9), 156 (100), 140 (23.6). HRMS exact mass calculated for $[M]^+$ $C_{14}H_{27}NO$ 257.1991, found 257.1990.

Photolysis with Fp Dimer with 1-Phenethyl Bromide: Coupling of the 1-Phenethyl Radical with TEMPO To Prepare 1-(2,2,6,6-Tetramethylpiperidinyloxy)-1-phenylethane (1). Following the procedure of Thoma,[12] (1-bromoethyl)benzene (136 mL, 1.00 mmol), TEMPO (312.5 mg, 2.00 mmol), and cyclopentadienyliron dicarbonyl dimer (530.5 mg, 1.49 mmol) were suspended in 10 mL of methanol, and the suspension was irradiated with a 400 W Osram Powerstar HQI-T Daylight lamp. The reaction was monitored by TLC. After 6 h, starting material had been consumed. Irradiation was stopped, and the solvent was reduced under vacuum. The residue was diluted with diethyl ether and filtered through Celite, and the solvent was removed *in vacuo* to give 0.6286 g of brown solid. Flash chromatography using a hexane−ethyl acetate gradient yielded two fractions containing the title compound: 21.8 mg of clear oil (8.3%), which was analytically pure, and an additional 147.0 mg of yellow oil of product, which showed broadened peaks in the ^{1}H-NMR spectrum due to a slight iron impurity (a total of 65% yield).

Photolytic Addition of Phenylthiyl Radical to Styrene: Coupling with TEMPO To Give 1-(2,2,6,6-Tetramethylpiperidinyloxy)-1-phenyl-2-(phenylthio)-ethane (9). A mixture of TEMPO (88.8 mg, 0.568 mmol), diphenyl disulfide (93.3 mg, 0.427 mmol), and freshly distilled styrene (0.66 mL, 5.7 mmol) was dissolved in 5.7 mL of deoxygenated benzene and photolyzed with a 275 W General Electric Sunlamp for 2.5 h until TEMPO was no longer visible by TLC. Volatiles were removed in vacuo, and the resulting mixture was purified by flash column chromatography (20 mm column, 99:2 hexane−ethyl acetate as the solvent) to afford 19.2 mg (9% yield) of the product as a slightly yellow oily solid. TLC: 98:2 hexane−ethyl acetate, UV, I_2, R_f = 0.19. IR ($CDCl_3$): 2934, 1480, 1376, 1261, 1095, 1026 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.32−7.22 (m, 10H), 4.81 (dd, 1H, J = 9.7, 3.9 Hz), 3.77 (dd, 1H, J = 12.3, 3.9 Hz), 3.23 (dd, 1H, J = 12.3, 9.7 Hz), 1.49−1.1 (m, 6H), 1.27 (br s, 3H), 1.18 (br s, 3H), 1.01 (br s, 3H), 0.65 (br s, 3H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 141.6 (quaternary), 132.0 (quaternary), 129.5 (CH), 128.8 (CH), 128.0 (CH), 127.7 (CH), 125.9 (CH), 85.2 (CH), 60.0 (quaternary), 40.5 (CH_2), 39.5 (CH_2), 34.5 (CH_3), 34.4 (CH_3), 20.5(2xCH_3), 17.2 (CH_2).

Photolysis of TEMPO with Di-*tert*-butyl Peroxide in THF To Prepare 2-(2,2,6,6-Tetramethyl-1-piperidinyloxy)tetrahydrofuran (11). In an oven-dried quartz reaction vessel equipped with a stir bar were combined tetrahydrofuran (4.3 mL, 52.960 mmol), TEMPO (0.2020 g, 1.293 mmol), and di-*tert*-butyl peroxide (0.470 mL, 2.558 mmol). The vessel was cleared of oxygen with a stream of nitrogen and then irradiated with a medium pressure mercury lamp at room temperature for 21 h until the reaction mixture was colorless. The mixture was diluted with 30 mL of diethyl ether, washed once with 10 mL of water and twice with 8 mL of saturated aqueous sodium bisulfite, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.2741 g of a pale yellow oil. Purification by flash column chromatography (2 cm, 98:2 hexane−ethyl acetate) yielded 0.162 g (55% yield) of the product as a yellow oil, containing trace impurities by NMR. TLC: 98:2 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.15. IR ($CDCl_3$): 2931, 2238, 1461, 1361, 1249, 1184, 1061 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 5.36 (q, 1H) 3.80−3.90 (m, 2H), 1.70−2.0 (m, 4H), 1.47 (br m, 5H), 1.40 (m, 1H), 1.21 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 109.6 (CH), 66.6 (CH_2), 60.1 (quaternary), 58.6 (quaternary), 40.1 (CH_2), 39.7 (CH_2), 34.0 (CH_3), 33.4 (CH_3), 31.2 (CH_2), 23.9 (CH_2), 20.4 (CH_3), 20.1 (CH_3), 17.3 (CH_2). Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.7; H, 11.1; N, 6.2. Found: C, 68.60; H, 10.91, N, 6.36.

Photolysis of TEMPO with Di-*tert*-butyl Peroxide in THF at Low Temperature to Prepare 2-(2,2,6,6-Tetramethyl-1-piperidinyloxy)tetrahydrofuran (11). The above reaction was carried out at −78 °C for 30 h in 50% yield.

Photolysis of TEMPO with Di-*tert*-butyl Peroxide in Diethyl Ether To Give 1-(2,2,6,6-Tetramethylpiperidinyloxy)-1-ethoxyethane (12). In a regular Pyrex flask were put TEMPO (0.1340 g, 0.858 mmol), diethyl ether (2.9 mL), and di-*tert*-butyl peroxide (3.15 mL, 1.72 mmol); the mixture was irradiated with a medium-pressure mercury lamp for 48 h at room temperature. The reaction mixture was diluted with 20 mL of ether and washed consecutively with 10 mL of water followed by 2 × 10 mL of saturated sodium bisulfite solution. The organic phase was dried over magnesium sulfate, and volatiles were removed *in vacuo* to give the product directly as 0.0774 g of yellow oil (39% yield). TLC: 6:1 hexane−ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.75. IR ($CDCl_3$): 2948, 1452, 1364, 1046 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 4.88 (q, 1H, J = 5.5 Hz), 3.74 (dq, 1H, J = 9.2, 7.1 Hz), 3.55 (dq, 1H, J = 9.2, 7.1 Hz), 1.70−1.40 (m, 6H), 1.46 (br s, 3H), 1.28 (d, 3H, J = 5.5 Hz), 1.22 (br s, 3H), 1.15 (t, 3H, J = 7.1 Hz), 1.10 (br s, 3H), 1.08 (br s, 3H). ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 104.9 (d), 62.8 (t), 60.5 (s), 59.1 (s), 40.4 (t), 40.1 (t), 33.6 (q), 33.6 (q), 20.5 (q), 20.0 (q), 19.2 (q), 17.3 (t), 15.3 (q).

Thermal Reaction of TEMPO and Di-*tert*-butyl Hyponitrite in THF To Prepare 2-(2,2,6,6-Tetramethyl-1-piperidinyloxy)tetrahydrofuran (11). Di-*tert*-butyl hyponitrite (1.20 g, 6.89 mmol) and TEMPO (0.7065 g, 4.522 mmol) in 15.2 mL of tetrahydrofuran were heated at 50 °C for 2 days. Volatiles were removed *in vacuo* to yield 1.4459 g of a dark yellow oil. Purification by flash column chromatography (5 cm, hexane−ethyl acetate gradient) yielded 0.8608 g of the product as a clear yellow oil (78.5%).

Thermal Reaction of TEMPO, Phthalide, and Di-*tert*-butyl Hyponitrite To Prepare 3-(2,2,6,6-Tetramethyl-1-piperidinyloxy)phthalide (13). Following the procedure of Mendenhall,[13] phthalide (0.5067 g, 3.778 mmol), di-*tert*-butyl hyponitrite (0.3640 g, 2.089 mmol), and TEMPO (0.5923 g, 3.791 mmol) were dissolved in 0.9 mL of benzene, and the solution was heated at 50 °C for 2 days. Volatiles were removed *in vacuo* to yield a thick red oil and washed with cold hexane to precipitate unreacted phthalide. Purification by flash column chromatography (4 cm, hexane−ethyl acetate gradient) yielded 0.0423 g of yellow oil, which was further purified by preparative TLC to afford 0.0091 g of the pure product as a yellow oil in addition to 0.0881 g of a slightly impure product (8.9% yield). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.71−7.89 (m, 4H), 6.70 (s, 1H), 1.59 (br s, 6H), 1.45 (s, 3H), 1.38 (s, 3H), 1.26 (s, 3H), 1.06 (s, 3H); ^{13}C-NMR (APT) (63 MHz, $CDCl_3$): δ 168.7 (quaternary), 144.5 (quaternary), 134.2 (CH), 130.8 (CH), 127.9 (CH), 125.4 (CH), 123.7 (CH), 106.6 (CH), 61.5 (quaternary), 59.9 (quaternary), 40.4 (CH_2), 40.1 (CH_2), 34.3 (CH_3), 33.4 (CH_3), 20.6 (CH_3), 20.4 (CH_3), 17.1 (CH_2).

Results and Discussion

Nitroxides are kinetically persistent radicals commonly prepared by the oxidation of doubly *N*-neopentylhydroxylamine precursors. Oxidative methods for

Scheme 1

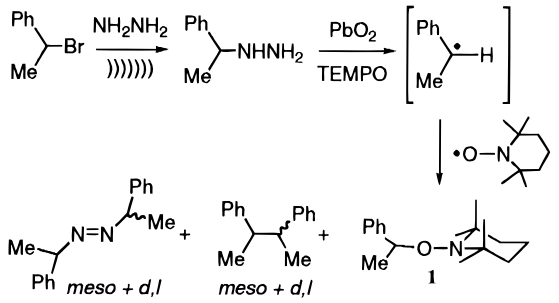
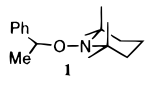
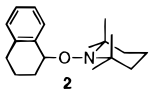
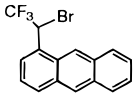
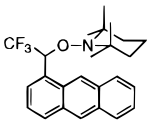
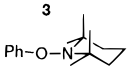
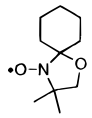
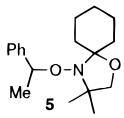
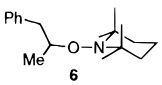


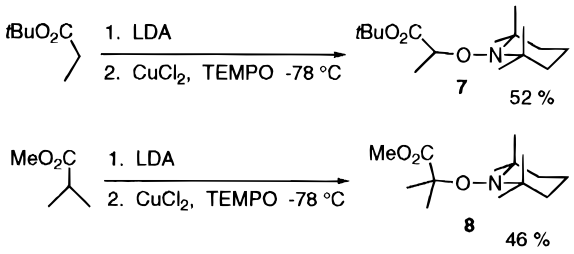
Table 1. Alkyl Bromides Converted to Hydrazines, Oxidized by PbO_2, and Trapped with Nitroxides

SM	Nitroxide	Product	Temp.	Yield[a]
	 (TEMPO)	 1	-78 °C	78%
	TEMPO	 2	-78 °C	22%
	TEMPO	 3	RT	23%
Ph-NHNH$_2$[b]	TEMPO	 4	RT	16%
		 5	-78 °C	60%
	TEMPO	 6	-78 °C	30%

[a] Yields are unoptimized. [b] Purchased from Aldrich.

generating transient carbon radicals in the presence of nitroxide traps requires a mild oxidant that will not competitively further oxidize the nitroxide. Lead dioxide effectively oxidizes alkylhydrazines to dinitrogen and alkyl radicals.[14] However, many alkylhydrazines are of marginal stability and are difficult to handle. We have developed a simple two-step procedure involving the preparation of alkylhydrazines using a straightforward S_N2 displacement of benzyl or alkyl bromides with neat hydrazine followed promptly by generation of the carbon radical with lead dioxide in the presence of the nitroxide trap (Scheme 1). A 20-fold excess of fuming hydrazine is utilized to minimize hydrazine dialkylation; sonication is used to mix the organic substrate with the polar hydrazine layer. As soon as the sonicated mixture becomes a homogeneous opaque layer, addition of diethyl ether and an aqueous workup removes excess hydrazine. The alkylhydrazine (used in at least 2 mol excess) is then dissolved in toluene and the solution cannulated into a solution of the nitroxide and at least 2 equiv of lead dioxide.[15] Following the coupling reaction, dilution with diethyl ether minimizes migration of the lead residues upon filtration through Celite. The monomeric initiator **1** is obtained following purification by silica gel chromatography. A number of examples of coupling using this methodology are shown in Table 1. A small amount of carbon radical self-dimerization product is generally formed but is easily removed as a nonpolar byproduct, eluting from the silica column within the first fractions. In some cases, small amounts of a diazo compound are formed, presumably from dialkylation of the hydrazine in the nucleophilic displacement reaction, followed by oxidation by lead dioxide. Bromide starting materials other than 1-phenethyl bromide and 1-phenyl-2-bromopropane were prepared from the corresponding alcohols using the bromine + DIPHOS procedure of Schmidt and Brooks,[8] which utilizes 1,2-bis(diphenylphosphino)-ethane (DIPHOS) in place of the more commonly utilized triphenylphosphine. This method is advantageous for the preparation of these sensitive benzylic bromides, as the phosphine oxide byproduct is removed by a simple precipitation, filtration procedure.

Scheme 2



As there are some misconceptions about the NMR spectra of these compounds in the literature,[5] it should be noted that the stereogenic center at the benzylic position causes all four of the TEMPO-derived methyl groups to be diastereotopic. These four methyl groups are very clearly differentiated in the ^{1}H-NMR, with chemical shifts of δ 1.30, 1.17, 1.02, and 0.66 ppm for compound **1**. In addition, each of the piperidino ring carbons are diastereotopic; in some cases they are seen as distinct peaks in the ^{13}C-NMR spectra.

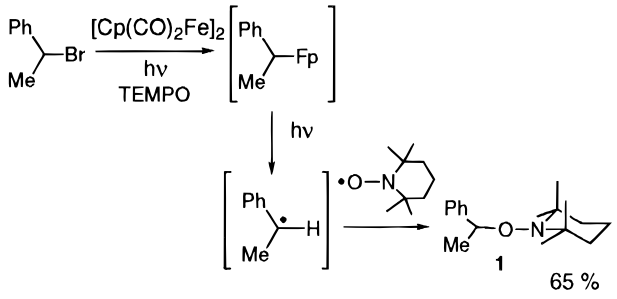
This alkylhydrazine−lead dioxide methodology is effective with a variety of nitroxides[16] in addition to TEMPO. For example, the doxyl radical derived from cyclohexanone can be used to prepare the 1-phenethyl initiator **5**. This reaction has been carried out on a gram scale.

The ease of alkylhydrazine formation in the displacement reaction of the bromide starting material is the limiting constraint in utilizing this method. In addition to benzylic bromides, phenyl radical was trapped to prepare product **4**, whereas the last example in Table 1 illustrates use of this method with a regular secondary alkyl bromide to form the nitroxide-coupled product **6** in moderate yield.

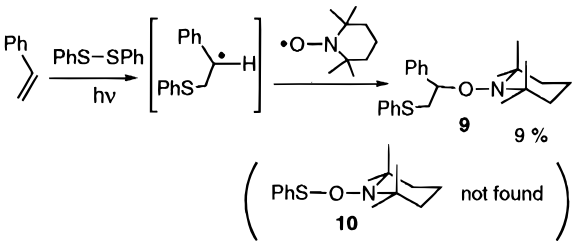
An alternative method for the generation of carbon radicals under oxidative conditions is the metal-mediated oxidation of carbon anions by salts of copper[17] or iron.[18] In particular, copper(II) oxidation of lithium enolates has been a very popular method of effecting dimerizations, although Porter has recently demonstrated that this process does not involve the dimerization of two truly free carbon radicals but is possibly a free radical addition to an enolate.[19] We have found that copper(II)-mediated oxidation of lithium enolates in the presence of TEMPO is an effective method of preparing monomeric initiators bearing a carbonyl group adjacent to the *N*-oxy-coupled position (Scheme 2). The use of *tert*-butyl propionate provides the coupling product **7**, whereas generation of the enolate from methyl isobutyrate gives initiator **8**. This should prove particularly useful in the polymerization of methyl methacrylate.

Photolytic methods of carbon radical generation are an obvious alternative to thermal radical generation

Scheme 3



Scheme 4



techniques. Despite the known ability of UV-photoexcited TEMPO to function as an efficient hydrogen abstractor,[20] photochemical methods can be utilized to generate carbon radical/nitroxide trapping products. We first examined the use of "the iron method"[21] developed by Giese and Thoma,[22] in which cyclopentadienyliron dicarbonyl dimer ("Fp dimer") is photolyzed in the presence of a benzylic bromide to give an intermediary benzylic organoiron species (Scheme 3). Continued irradiation results in fragmentation to give a benzylic carbon free radical, which can be intercepted by TEMPO. Although the yield is good, purification of the product requires careful chromatography to remove the multiple paramagnetic iron side products.

Photolytic generation of thiyl radical by cleavage of diphenyl disulfide followed by addition to styrene was also investigated as a mild, low-temperature route to carbon radical formation. In previous reports, hydrogen abstraction from thiol by 1 equiv of nitroxide to give thiyl radical, addition to an olefin, and subsequent trapping by a second equivalent of nitroxide has been demonstrated, although no chemical yields were given.[23] We chose to use the disulfide (Scheme 4) in order to avoid the presence of thiol, an excellent hydrogen donor that could potentially reduce the nitroxide to the hydroxylamine as well as donate hydrogen to the intermediary carbon radical. In a somewhat optimized reaction, the desired product **9** was formed, accompanied by a number of impurities. Chromatography provided the pure product in 9% yield. Notably, none of the thiyl–TEMPO trapping product **10** was isolated, whereas the analogous compound was reported to be frequently isolated when thiols were utilized. Deoxygenation of TEMPO by arene thiols has recently been found to be a major product in these reactions.[24]

The use of oxygen-centered radicals to generate carbon radicals followed by nitroxide trapping is a common procedure, as they do not react competitively with the nitroxide trap. Oxygen radicals can be added to olefins to give intermediary carbon radicals,[25] or they can be used to abstract activated hydrogens from carbon substrates (Scheme 5). Often these reactions have been carried out at relatively high temperatures, conditions at which the products themselves are only marginally stable. We have utilized the hydrogen abstraction route

Scheme 5

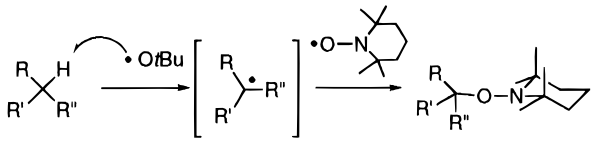
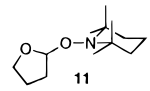
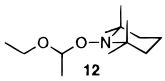
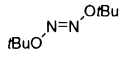
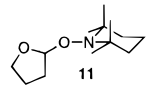
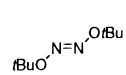
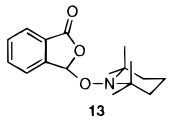


Table 2. Hydrogen Abstraction Followed by Coupling of the Carbon Radical with TEMPO

substrate	technique	Product	conditions	Yield[a]
THF	hν, *t*BuO–O*t*Bu	 11	quartz RT, 21 h quartz -78 °C, 30 h pyrex RT, 14 h	55 % 50 % ≈100 %
Et_2O	hν, *t*BuO–O*t*Bu	 12	pyrex RT, 2 days	39 %
THF		 11	50 °C, 2 days	78 %
		 13	50 °C, 2 days	9 %

[a] Yields are unoptimized.

under both photochemical and mild thermal oxygen radical generating conditions (Table 2). The photolytic generation of *tert*-butoxy radical from di-*tert*-butyl peroxide is attractive in that it can be carried out at either ambient temperatures or at −78 °C. Previous reports have demonstrated this technique using either laser flash photolysis[26] or, on a preparative scale, a Rayonet photolysis apparatus.[7b] In this work, the light source was a medium-pressure mercury lamp. The use of Pyrex gave better yields and cleaner reactions than the use of quartz reaction vessels. Whereas the reaction worked very well using tetrahydrofuran or diethyl ether as substrate and solvent, these conditions were not successful with a variety of potential substrates that could not be used in huge excess as solvent.

Alternatively, thermal generation of *tert*-butoxy radicals from relatively low temperature initiators is an option. Busfield has reported the use of di-*tert*-butyl peroxyoxalate at 40–60 °C to abstract allylic hydrogens from olefin substrates in the presence of a nitroxide trap.[27] We chose to use the safe and easily prepared di-*tert*-butyl hyponitrite popularized by Mendenhall[28] to generate the *tert*-butoxy radical at 50 °C. We initially examined tetrahydrofuran as the substrate and obtained a 78% yield of the TEMPO-trapped product. However, extending this reaction to phthalide in benzene (a reaction reported by Mendenhall[29]) provided the product in a disappointing 9% yield. It is clear that this technique is useful for low-boiling, inexpensive substrates bearing easily abstractable hydrogen atoms but will be of limited utility for more specialized substrates if a high yield is desired.

In summary, a number of new methodologies have been developed to prepare unimolecular nitroxide initiators under mild, low-temperature conditions. These methods expand the repertoire of available procedures for the preparation of a variety of initiators for living free radical nitroxide polymerizations. Of particular interest, the copper-mediated oxidation of ester enolates allows for preparation of unimolecular nitroxide initiators for acrylate polymerizations.

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