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Synthesis of Functionalized Bidirectional Initiator Using Atom Transfer Radical Addition

Gabriel Overholtzer
Jean Reuhl
Dr. Rebecca Braslau

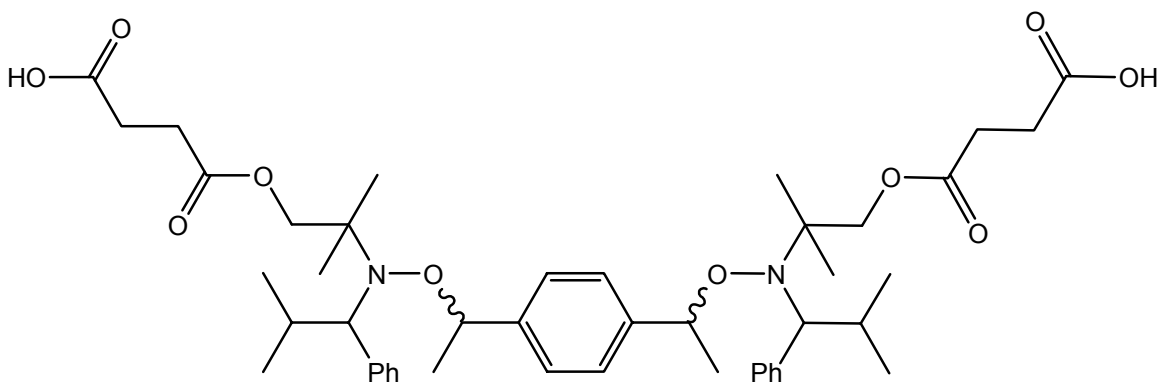
UC Santa Cruz

Table of Figures/Schemes

Figure 1. Functionalized Bidirectional Initiator.....	3
Scheme 1. Synthesis of Braslau-Vladimir Nitroxide.....	4
Scheme 2. Synthesis of α,α' -dibromo-1,4-diethylbenzene.....	4
Scheme 3. Synthesis of Model Alkoxyamine.....	5
Scheme 4. Model Study Using PMDETA.....	6
Scheme 5. Use of 5 as Substrate.....	6
Scheme 6. Synthesis of THP-nitroxide.....	7
Scheme 7. Functionalized Alkoxyamine.....	8
Scheme 8. Functionalized Bidirectional Initiator.....	8

Table of Contents

Abstract:.....	3
Introduction.....	3
Results.....	4
Conclusions.....	9
Experimentals.....	9
References:.....	14



1.

Figure 1. Functionalized Bidirectional Initiator

Abstract:

The synthesis of previous alkoxyamines using Jacobsen’s catalyst has presented difficulty. Herein, the synthesis of an alkoxyamine functionalized bidirectional initiator is developed using atom transfer radical addition.

Introduction

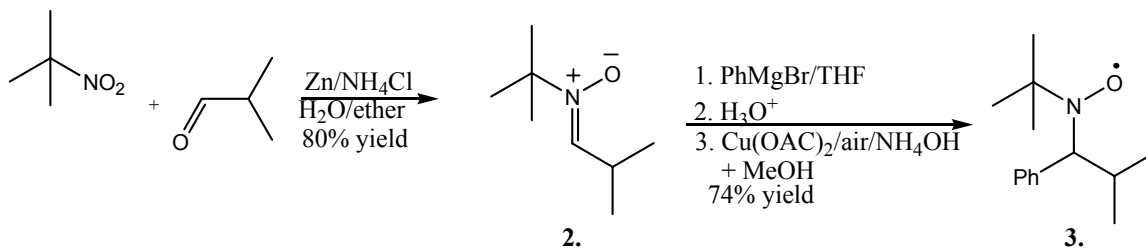
Polymers are evident in virtually every area of nature. For example, DNA is simply a polymer consisting of four monomers. Among many applications, the development of polymerization techniques allows chemists to mimic biological structures. “Living” polymerization describes a technique that utilizes the reversible termination of a growing polymer chain to reduce the concentration of the propagating radical chain end. Therefore, polymer chains are initiated from the desired reactive intermediate and polymer growth occurs in a living i.e. controlled fashion. The use of living polymerization results in polymers with low polydispersities. Nitroxide mediated radical polymerization (NMRP) is a versatile form of living polymerization that can be used for the polymerization of a wide variety of monomer families such as acrylates, acrylamides, 1,3-dienes, and acrylonitrile based monomers¹.

The use of living polymerization techniques has been successfully used for the self-assembly of amphiphilic diblock copolymers into micelles². Wooley and coworkers have found that polymer micelles can act as multivalent antigen presenters—thereby illustrating the potential to function as synthetic vaccines³. Herein, we report the

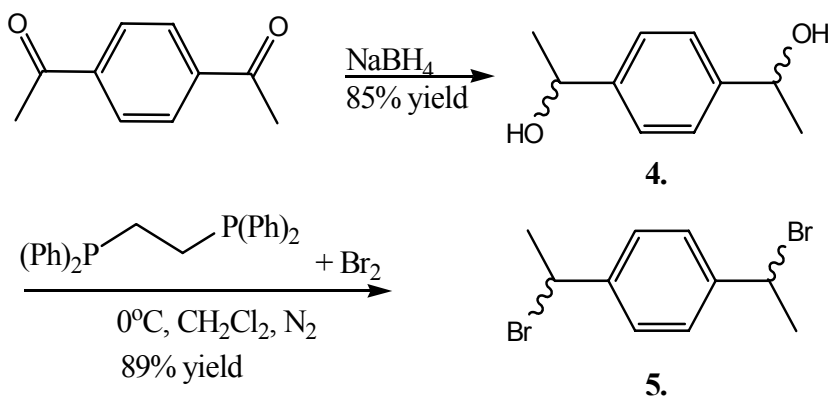
synthesis of a functionalized bidirectional initiator (**1**) by atom transfer radical addition. The use of a functionalized bidirectional initiator will enable the synthesis of functionalized triblock copolymers. Low polydispersity is encouraged by both polymer chains being grown simultaneously and the carboxylic acid functional group can be displaced by a wide array of agents for future applications.

Results

A model study of the synthesis of **1** (Figure 1) was accomplished by first synthesizing the two substrates **3** (Scheme 1) and **5** (Scheme 2). The Braslau-Vladimir nitroxide (**3**) was synthesized in a known manner⁴ in good yields. The mild conditions developed by Schmidt and Brooks⁵ for converting alcohols to their corresponding halides was modified by using 1,4-Bis(1-hydroxyethyl)benzene (**4**) rather than 1-phenyl-ethanol. The byproducts of Scheme 2 simply crashed out of solution upon the addition of ether and pentane to give **5** in excellent yields.



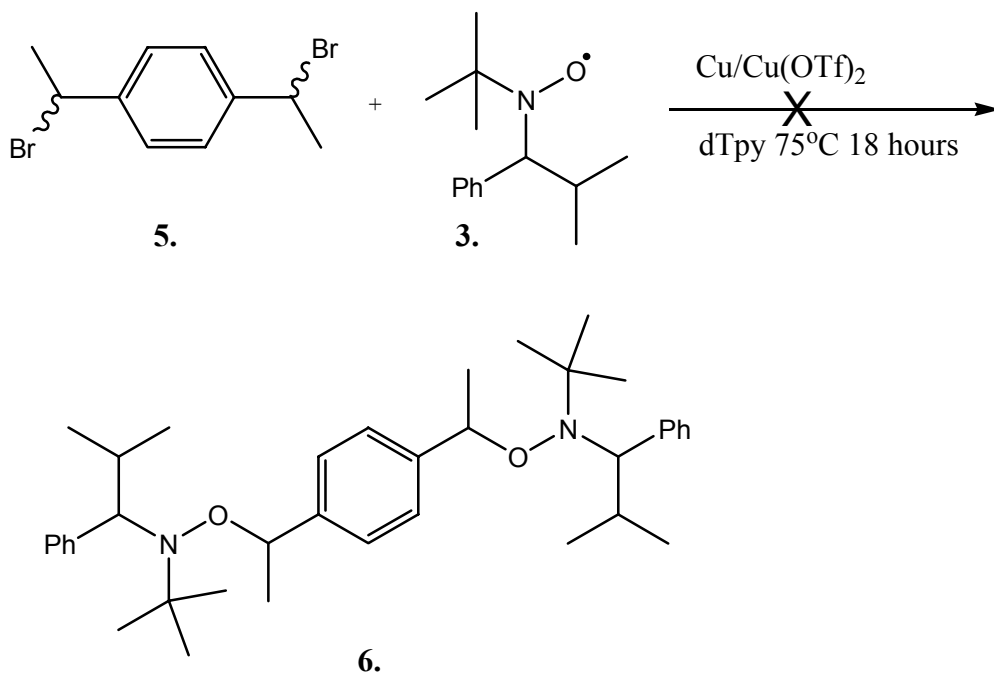
Scheme 1. Synthesis of Braslau-Vladimir Nitroxide



Scheme 2. Synthesis of α,α' -dibromo-1,4-diethylbenzene

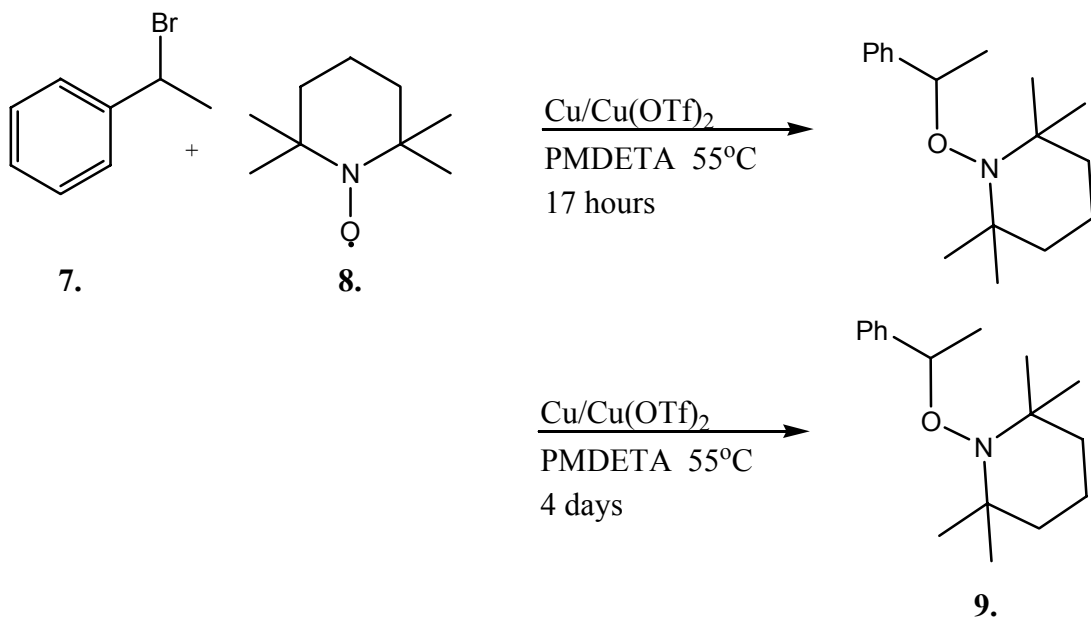
The synthesis of **6** (Scheme 3) by radical transfer radical addition (RTRA) was accomplished by adopting the methodology developed by Matyjaszewski *et al*⁶; however, the conditions were not suitable for the reactants used. ¹H NMR illustrated elimination

taking place to form styrene rather than **6**. It was speculated that the ligand, 4,4'-*tert*-butyl-2-2'-bipyridine (dTpy), was enabling the production of styrene.



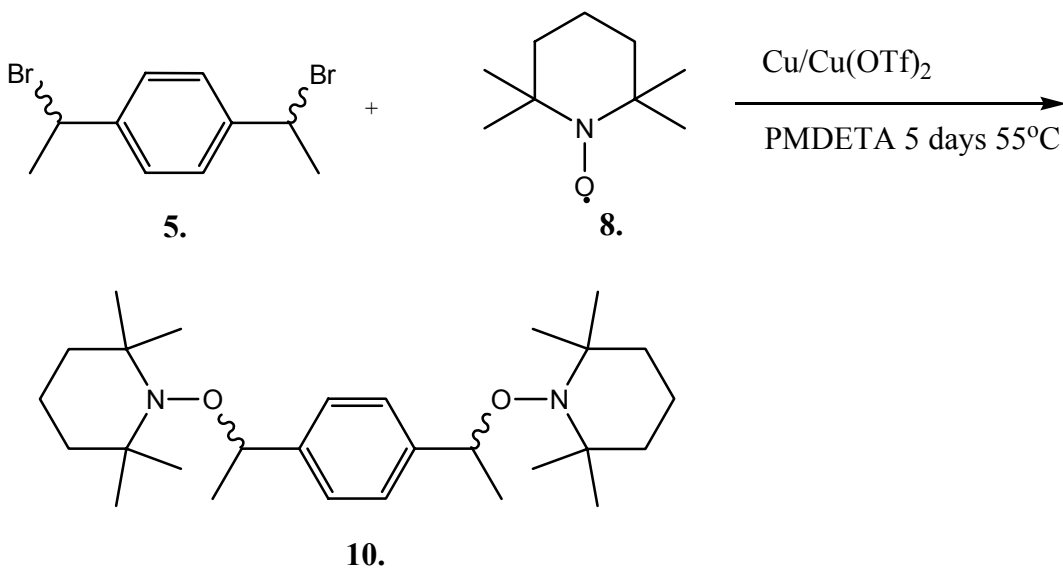
Scheme 3. Synthesis of Model Alkoxyamine

Therefore, a model study using pentamethyldiethylnetriamine (PMDETA) as the ligand for RTRA using (1-bromo)-ethyl benzene (**7**) and tetramethylbipyridinidoxy (**8**) as the model substrates was accomplished (Scheme 4).



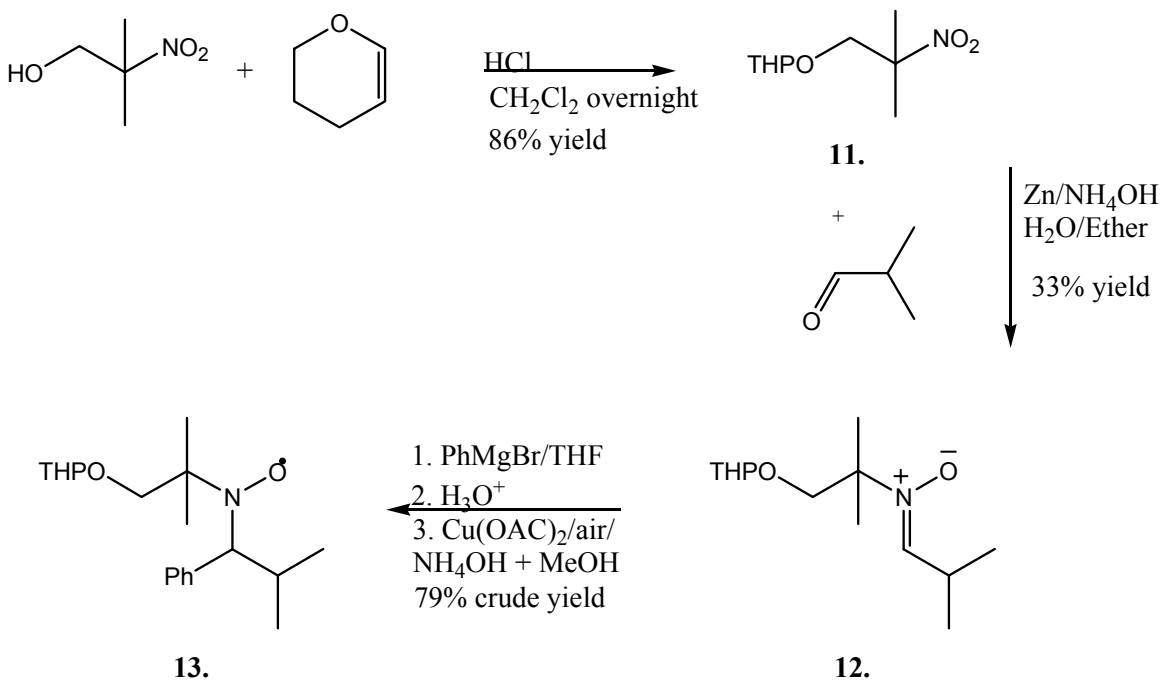
Scheme 4. Model Study Using PMDETA

PMDETA has been successfully used for analogous coupling reactions at lower temperatures. By utilizing a lower temperature (55°C), the production of styrene was eliminated. The reaction time was extended to four days to allow for the complete consumption of **7**. The optimized conditions afforded **9** in clean form. The synthesis of **9** was followed by using α,α' -dibromo-1,4-diethylbenzene (**5**, Scheme 5) as a substrate to determine if different conditions were needed. After 5 days, **10** was obtained in nearly pure form.



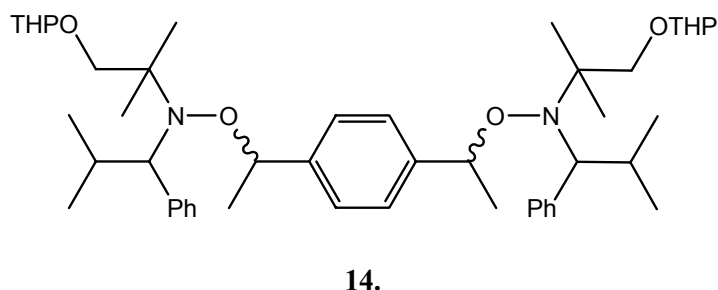
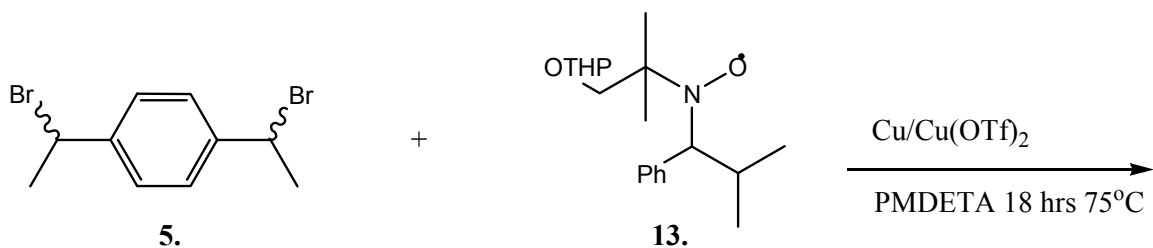
Scheme 5. Use of 5 as Substrate.

The improved methodology indicated that further model studies were unnecessary. Subsequently, the synthesis of **13**, a THP protected nitroxide, was synthesized (Scheme 6) for use in the production of **1**. All steps leading up to the synthesis of **13** were successful; however, ^1H NMR showed that **13** was obtained with significant inseparable byproducts.



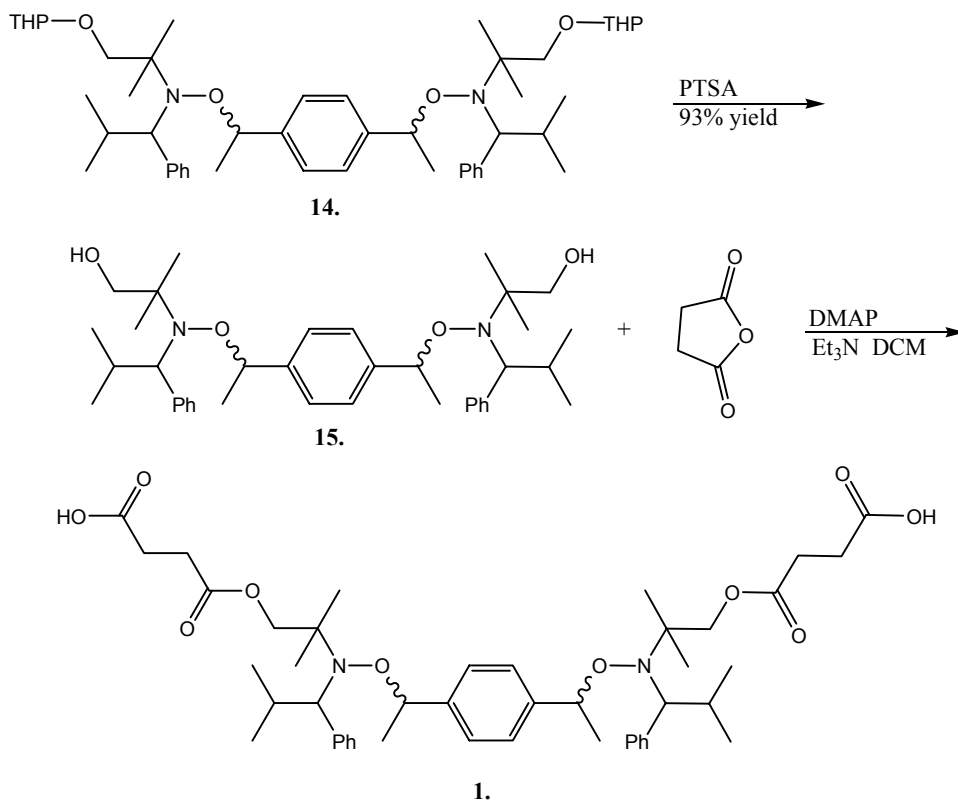
Scheme 6. Synthesis of THP-nitroxide

A pure form of **13** was obtained (**JW745**) and the synthesis of **1** was attempted (Scheme 7) using the newly optimized conditions of a higher temperature (75°C) which enabled a reaction time of 18 hours. The reaction produced a mixture of the mono-directional as well as the bidirectional alkoxyamine with diastereomers of each. **13** was easily separated from the crude mixture with the distinct $R_f = 0.3$ (95:5 hexanes/ethyl acetate) whereas the mono-directional version of **13** was $R_f = 0.4$.



Scheme 7. Functionalized Alkoxyamine

The THP-protected alkoxyamine **14** was deprotected by the addition of *p*-toluenesulfonic acid and carboxylic acids were attached by the addition of succinic anhydride (Scheme 8).



Scheme 8. Functionalized Bidirectional Initiator

Conclusions

A viable method for the synthesis of alkoxyamine functionalized bidirectional initiators using ATRA has been developed. Further work will include the characterization of **14**, **15**, and **1** by mass spectrometry, ^{13}C NMR, and the use of **1** in NMRP as well as displacing the carboxylic acids with phosphatidylcholines.

Experimentals

N-tert-butyl- α -iso-propylnitrone (**2**)

A 100 ml round-bottomed flask was charged with 2-methyl-2-nitropropane (2.0g), isobutyraldehyde (2.1g), 40 ml of water, and 20 ml of ether before cooling to 0°C. Ammonium chloride (1.1g) and zinc (5.17g) was added and the mixture was stirred for 4 hours before being poured into a sintered glass filter packed with celite. The filtered mixture was extracted with four portions of methylene chloride and once with brine. The product was dried over MgSO_4 , filtered, and concentrated *in vacuo* to afford 2.3g product (80.5% yield). ^1H NMR (500 MHz CDCl_3) δ : 6.63 (d, J = 6.5 Hz, 1H), 3.2 (m, 1H), 1.49 (s, 9H), 1.1 (d, J = 10.5 Hz, 6H).

2,2,5-Trimethyl-4-phenyl-3-azahexane-3-nitroxide (**3**)

N-tert-butyl- α -iso-propylnitrone was dissolved in 10 ml of dry THF in a 50 ml round-bottomed flask under Nitrogen. The mixture was cooled to 0°C and 6.5 ml of 3M phenylmagnesium bromide was added. The mixture was stirred for 12 hours before 2 ml of concentrated NH_4Cl was added followed by 10 ml of water to dissolve all solids. The organic layer was separated and the aqueous layer was extracted with 4X20 ml of ether. The organic layers were combined, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo* before the addition of 75 ml MeOH, 7 ml concentrated NH_4OH , and 157 mg of $\text{Cu}(\text{OAc})_2$. Air was bubbled through the mixture for 7 minutes causing the mixture to turn from yellow to green. The mixture was concentrated under vacuum than dissolved in 70 ml chloroform, 70 ml water, and 20 ml of concentrated NaHSO_4 . The organic layer was separated and the aqueous layer was extracted with 4X20 ml chloroform. The organic layers were combined, washed with saturated Na_2CO_3 , dried over MgSO_4 , filtered and concentrated before purification with 9:1 hexane/EtOAc on a 5

cm column to give 2.8g (87%) of the product as an orange oil. ^1H NMR (500 MHz CDCl_3) δ : 7.41 – 7.20 (m, 5H), 3.23 (d, $J = 9.8$ Hz, 1H), 2.31 (m, 1H), 1.18 and 0.63 (two d, $J = 6.5$ Hz, 6H), 0.90 (s, 9H).

1,4-Bis(1-hydroxyethyl)benzene (4)

A 250 ml round-bottomed flask was charged with 2g of p-diacetylbenzene dissolved in 100 ml isopropyl alcohol before the addition of 1.3 g NaBH_4 . The yellow mixture was stirred overnight. The mixture was concentrated *in vacuo* then dissolved in 50 ml CH_2Cl_2 and 50 ml of water then separated. The aqueous layer was extracted with 4X25 ml CH_2Cl_2 than washed with brine, dried over K_2CO_3 , filtered and concentrated. Purification by flash chromatography using 7:3 dichloromethane/acetone afforded 1.8g (85%) of the white solid product TLC 80:20 ethyl acetate/hexanes, $R_f = 0.62$. ^1H NMR (500 MHz CDCl_3) δ : 7.36 (s, 4H), 4.89 (q, $J = 6$ Hz, 2H), 1.88 (broad s, 2H), 1.49 (d, $J = 6$ Hz, 6H).

α,α' -dibromo-1,4-diethylbenzene (5)

This reaction utilized distilled CH_2Cl_2 and was conducted under N_2 . A 250 ml round-bottomed flask was charged with 2.6g 1,2-bis(triphenylphosphino)ethane dissolved in 100 ml CH_2Cl_2 followed by the addition of 0.7 ml Br_2 dissolved in 10 ml of CH_2Cl_2 . The mixture was cooled to 0°C before the addition of 875mg of above diol dissolved in CH_2Cl_2 . The mixture was allowed to warm to room temperature and stirred for two hours. Byproducts were precipitated by the addition of 100 ml of ether and 200 ml of pentane. The mixture was filtered over a thin pad of silica and the solids were washed with 2X30 ml of 1:2 ether/pentane to afford 1.38g (89%) of the solid white product. ^1H NMR (500 MHz CDCl_3) δ : 7.42 (s, 4H), 5.2 (q, $J = 1$ Hz, 2H), 2.0 (d, $J = 7$ Hz, 6H).

2,2,6,6-Tetramethyl-1-(1-phenyl-ethoxy)-piperidine (9)

(1-bromo)-ethyl benzene (0.5g), tetramethylbipyridinidoxy (0.5g), copper (0.172g), copper(II) trifluoromethane sulfonate (0.01g), pentamethyldiethylnetriamine (0.019g), and 15 ml of benzene were added to a 25 ml round-bottomed flask and degassed under argon. The degassed solution was placed in a 55°C oil bath and stirred for 4 days. The reaction was discontinued by allowing the mixture to cool to 25°C . The solution was

filtered through an activated neutral alumina plug and concentrated. ^1H NMR was taken of the crude product without further purification. ^1H NMR (500 MHz CDCl_3) δ : 7.38-7.20 (m, 5H), 4.8 (q, $J = 6.5$ Hz, 1H), 1.56-1.35 (m, 6H), 1.50 (d, $J = 7$ Hz, 3H), 1.31 (s, broad, 3H), 1.18 (s, broad, 3H), 1.04 (s, broad, 3H), 0.67 (s, broad, 3H).

1,4-diethyloxy-Bis(*N*-2,2,6,6-tetramethyl piperidene)-benzene (10)

α,α' -dibromo-1,4-diethylbenzene (60 mg), tetramethylbipyridoxy (80 mg), copper (33 mg), copper(II) trifluoromethane sulfonate (2 mg), pentamethyldiethylnetriamine (3 mg), and 5 ml of benzene were added to a 15 ml glass ampule and degassed. The degassed solution was placed in a 55°C oil bath and stirred for 2.5 days. The mixture was allowed to cool to 25°C before being filtered through an activated neutral alumina plug packed in a 15 ml sintered glass filter. The crude product was concentrated and ^1H NMR was taken without further purification. ^1H NMR (500 MHz CDCl_3) δ : 7.6 – 7.2 (m, 4H), 4.8 (q, $J = 6.5$ Hz, 2H), 1.56-1.35 (m, 12H), 1.50 (d, $J = 7$ Hz, 6H), 1.31 (s, broad, 6H), 1.18 (s, broad, 6H), 1.04 (s, broad, 6H), 0.62 (s, broad, 6H).

2-(2-methyl-2-nitro-propoxy)-tetrahydro-pyran (11)

2-methyl-2-nitro-propan-1-ol (2g), 3,4-dihydro-2H-pyran (1.4g), and 13 ml of CH_2Cl_2 were added to a 50 ml round-bottomed flask. After the nitro compound dissolved 8 drops of concentrated HCl were added. A rubber septum and syringe were installed and the mixture stirred for 12 hours at room temperature. The mixture was poured into a separator funnel along with 25 ml of water. The organic layer was separated and the aqueous layer was extracted with 3X15 ml CH_2Cl_2 . The organic layers were combined and washed with 25 ml brine, dried over MgSO_4 and concentrated. The crude product was distilled on a Kugelrohr at 100°C to afford 3g (86%) of pure product. ^1H NMR (500 MHz CDCl_3) δ : 4.63 (t, $J = 3$ Hz, 1H), 3.98 and 3.71 (d, 2H, $J = 10$ Hz), 3.79 – 3.75 and 3.56 – 3.52 (two m, 2H), 1.77 – 1.49 (multiplets, 6H), 1.64 and 1.60 (two s, 6H).

***N*-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-*N*-isobutyl-nitrone, (12)**

11 (3g), isobutyraldehyde (2.1g), NH_4Cl (856 mg), 12 ml ether, and 25 ml water were added to a 100 ml round-bottomed flask and cooled to 0°C before slowly adding 3.8 g of

Zn. The ice was removed and a vented septum was installed. The mixture stirred overnight before being filtered through a celite plug to remove the Zn. The plug was washed with 5 ml MeOH and 15 ml ether. The organic layer was separated and the aqueous layer extracted with 3X20 ml CH₂Cl₂. The organic layers were combined, washed with 30 ml brine, dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography by using 500 ml pure ethyl acetate followed by 9:1 ethyl acetate/MeOH. The reaction afforded 1.2 g (33%) of the product as a clear liquid. ¹H NMR (500 MHz CDCl₃) δ: 6.64 (d, J = 7Hz, 1H), 4.61 (t, J = 3 Hz, 1H), 3.84 – 3.79 and 3.56 – 3.48 (two m, 2H), 3.76 and 3.71 (d, J = 9.5 Hz, 2H), 3.20 (m, 1H), 1.85 – 1.4 (multiplets, 6H), 1.51 and 1.46 (two s, 6H), 1.12 and 1.11 (two d, 6H)

***N*-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-*N*-(2-methyl-1-phenyl-propyl)-nitroxide (13)**

All glassware and needles were flame dried and cooled under N₂ prior to use. **12** (1.167g) was dissolved in freshly distilled THF (15ml) and cooled to 0°C under N₂. 3M phenyl magnesium bromide (5 ml) was added dropwise and the reaction stirred for three days. The reaction was quenched by the addition of 10 ml NH₄Cl and 15 ml dionized H₂O until the white solid had dissolved. The organic layer was separated and the aqueous layer washed with 3X20 ml ether. The organic layers were combined, dried over MgSO₄, filtered and concentrated to give yellow oil. The crude product was mixed with 30 ml methanol, cupric acetate (76 mg) and concentrated NH₄OH (1 ml). Air was bubbled through the mixture for 10 minutes causing the color to change from yellow to green. The mixture was concentrated followed by the addition of 30 ml DCM, 30 ml H₂O, and 5 ml saturated NaHSO₄. The organic layer was separated and the aqueous layer extracted with 3X20 ml DCM. The organic layers were combined and washed with 25 ml saturated NaHCO₃, dried over MgSO₄, and concentrated to give an orange oil as the crude nitroxide. The crude nitroxide was purified by flash chromatography using 1L of pure hexanes followed by 4:1 hexanes/ethyl acetate until the product emerged. The reaction yielded 1.221g (79%); unfortunately, ¹H NMR was not conclusive and TLC showed signs of impurities (**13** R_f = 0.29; byproduct R_f = 0.25; 19:1 hexanes/ethyl acetate).

***N*-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-*O*-[1-(4-{1-*N*-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-*N*-(2-methyl-1-phenyl-propyl)-aminoxy]-ethyl}-phenyl)-ethyl]-*N*-(2-methyl-1-phenyl-propyl)-hydroxylamine (14)**

α,α' -dibromo-1,4-diethylbenzene (341 mg), thp nitroxide (885 mg), copper (186 mg), copper(II) trifluoromethane sulfonate (10 mg), pentamethyldiethylnetriamine (18 mg), and 25 ml of benzene were added to a 50 ml round-bottomed flask and degassed. The degassed solution was placed in a 75 °C oil bath and stirred for 16 hours. The mixture was allowed to cool to 25°C before being filtered through an activated neutral alumina plug packed in a 15 ml sintered glass filter. The crude product was purified by flash chromatography using 500 ml of pure hexanes, 400 ml of 98:2 hexanes/ethyl acetate, and 300 ml of 90:10 hexanes ethyl acetate (TLC R_f = 0.4) to afford 462 mg (50% yield). ^1H NMR (500 MHz CDCl_3) δ : 7.6 – 7.05 (m, 14H), 5.0 – 4.8 (mixture of q, 2H), 4.6, 4.57, 4.23, 4.09 (t, 2H), 3.94 – 3.20 (mixture of doublets and triplets, 10H), 2.36 (m, 2H), 1.9 – 1.57 (mixture of multiplets, 12H), 1.40 – 0.6 (mixture of s, d, 24H).

2-[[1-(4-{1-[*N*-(2-Hydroxy-1,1-dimethyl-ethyl)-*N*-(2-methyl-1-phenyl-propyl)-aminoxy]-ethyl}-phenyl)-ethoxy]-(2-methyl-1-phenyl-propyl)-amino]-2-methyl-propan-1-ol (15)

14 (462 mg), *p*-toluene sulfonic acid (22 mg), 20 ml of methanol, and 11 ml of tetrahydrofuran were added to a 100 ml round-bottomed flask. The mixture stirred for 19 hours before 3.3g NaHCO_3 was added to raise the pH to 7. The mixture was filtered, concentrated and purified by flash chromatography using 600 ml of 9:1 hexanes/ethyl acetate followed by 100 ml of 7:3 hexanes/ethyl acetate. The purification afforded 0.338g (93%) of **15** as a white sticky solid. ^1H NMR (500 MHz CDCl_3) δ : 7.6 – 7.0 (m, 14H), 5.0 – 4.8 (mixture of q, 2H), 3.7 – 2.6 (mixture of d, 8H), 2.41 (m, 2H), 1.66 – 1.57 (mixture of d, 6H), 1.36 – 0.18 (mixture of s, d, 24H).

Succinic acid mono-{2-[[1-(4-[*N*-(2-(3-carboxy-propionyloxy)-1,1-dimethyl-ethyl)-*N*-(2-methyl-1-phenyl-propyl)-aminoxy]-ethyl}-phenyl)-ethoxy]-(2-methyl-1-phenyl-propyl)-amino]-2-methyl-propyl}ester (1)

Triethylamine and dichloromethane were distilled prior to use. A 2-necked 50 ml round bottomed flask with stir bar was flame dried and cooled under N_2 . 4-Dimethylamino pyridine (9 mg) and succinic anhydride (142 mg) were added through the side arm.

Distilled DCM (15 mls) was used to transfer **15** (338 mg) into the reaction flask.

Triethylamine (0.8 ml) was syringed into the flask and the reaction stirred for 10 days.

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