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SANTA CRUZ

NITROXIDES: PROFLUORESCENT SENSORS AND FUNCTIONALIZED ALKOXYAMINE INITIATORS FOR NITROXIDE MEDIATED RADICAL POLYMERIZATION

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by

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Abstract

Nitroxides: Profluorescent Sensors and Functionalized Alkoxyamine Initiators for Nitroxide Mediated Radical Polymerization

Chittreeya Tansakul

Nitroxides have played a vital role in many areas in chemistry, due to their persistent radical nature, and facile redox properties. In this thesis, nitroxides are used to quench the fluorescence of organic fluorophores and quantum dots, as well as to prepare end-functionalized polymers using nitroxide mediated radical polymerization (NMRP).

Quantum dot (QD) fluorescence is effectively quenched by binding to functionalized nitroxides. The association constants and fluorescence quenching of CdSe QDs with nitroxides bearing a ligand coordinated to the QD surface have been examined using electron paramagnetic resonance and fluorescence spectroscopy. Quenching of QD fluorescence is dependent on the distance between the radical and the QD, and the binding affinity. The quenched fluorescence is restored when the surface-bound nitroxide is converted to a hydroxylamine by a mild reducing

agent, or trapped by a carbon radical to form an alkoxyamine. A fluorescence quenching mechanism is proposed.

The phenomenon of fluorescence quenching was extended to organic fluorophores. Nitroxides were synthesized bearing a tethered photosensitive species that undergo photocleavage to form a radical, which is then intramolecularly trapped by the nitroxide. When a fluorescent tag is appended to these nitroxides, the fluorescence is restored upon photoexcitation. A profluorescent nitroxide sensor of mild reductants was also developed, which undergo cyclization upon formation of the hydroxylamine. Unlike existing methodologies, this sensor is non-reversible since it cannot be reoxidized in the presence of oxygen.

Thiol-derivatized *N*-alkoxyamines, functionalized with a free thiol, disulfide, or trityl-protected thiol group were synthesized and employed in NMRP. Deprotection of the trityl group and mild oxidation provided disulfide linked polystyrene of double the molecular weight. Reduction of this polystyrene, followed by trapping with *N*-phenylmaleimide (NPM) resulted in a NPM-protected thiol terminated polystyrene with the same molecular weight as prior to oxidation.

This dissertation is dedicated to my beloved grandmother

Sewki Tansakul. It would not exist without her.

“God couldn’t be everywhere, so he made Grandmas.”

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that would make me enjoy thinking about organic chemistry in different ways. Erin Lilie have carried out a lot of work on EPR studies for my project, I appreciate her contribution. Aruna Earla and Friederike Schäffner made graduate school more fun than it would have been without them. In addition to being terrific labmates, we share food and a wonderful discussion about life.

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Chapter 1: Nitroxides in Synthetic Radical Chemistry: Oxidations

The review below constitutes part of a book chapter: C. Tansakul and R. Braslau (2012). Nitroxides in Synthetic Radical Chemistry in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, C. Chatgilialoglu and A. Studer (eds). John Wiley & Sons Ltd, Chichester, UK, pp 1095-1130.

1.1 Introduction

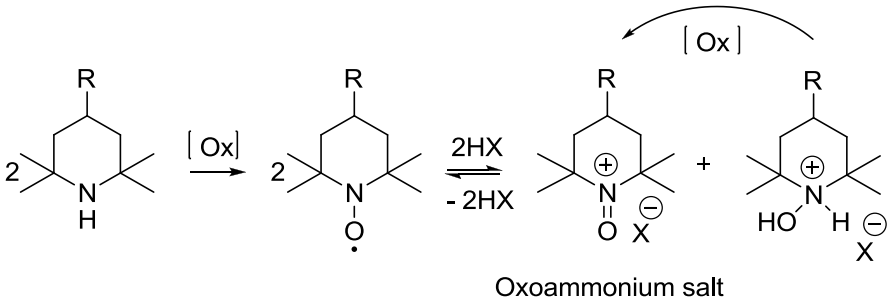
Oxidations using nitroxides are remarkably mild and chemoselective. Isomerizations of double bonds and stereogenic centers are rarely observed. Moreover, no heavy metals such as chromium or manganese are required. As a result, nitroxide-mediated oxidations are considered "green". Nitroxide radicals, especially TEMPO and derivatives, are easily converted to the corresponding oxoammonium cations, which are highly reactive oxidants. In addition to alcohol oxidations, oxoammonium species are utilized as one-electron oxidants with a variety of substrates, including sulfides, thiols, phenols and activated alkenes. Oxidations mediated by electron-poor nitroxides occur via hydrogen abstraction. Nitroxide-mediated oxidations have been covered in a number of reviews.[1-11]

1.2 Chemoselective oxidation of alcohols

Oxoammonium salts derived from nitroxides have been widely utilized in the oxidation of primary and secondary alcohols to the corresponding aldehydes, ketones and carboxylic acids. The oxoammonium salt can be pre-formed and used stoichiometrically. Alternatively, it can be generated *in situ* from acid-catalyzed disproportionation of nitroxide radicals or from oxidation of a catalytic amount of nitroxide with a stoichiometric cooxidant. Since nitroxides are effective radical scavengers, potential autooxidation of the aldehyde products is inhibited.[12]

1.2.1 Stoichiometric Oxoammonium Salts

There are reports of many structurally diverse oxoammonium salts;[1] however most oxidations have been carried out using piperidinyl nitroxide-derived species. Oxoammonium salts can be prepared by acid-catalyzed disproportionation of nitroxides,[13] which in turn are prepared by oxidation of the corresponding hindered amines (**Scheme 1.1**). Disproportionation leads to a 1:1 mixture of the oxoammonium salt and the corresponding hydroxyammonium salt. The latter can be oxidized *in situ* by hypohalites to form the oxoammonium salt or the nitroxide radical upon treatment with air. Alternatively, one-electron oxidation of nitroxide with halogen (Cl_2 or Br_2) or hypohalite gives oxoammonium cation with a halogen anion.[14] Use of bromine can result in bromide or tribromide as the counterion or a

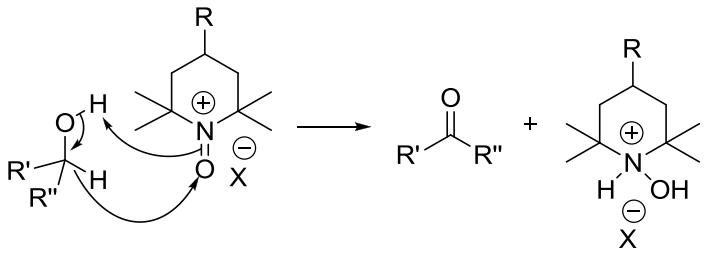


Scheme 1.1 Preparation of oxoammonium salts via oxidation of the corresponding hindered amines to the nitroxides, followed by acid disproportionation

mixture.[1] A side reaction is bromination of allylic alcohols.[14] Chloride as counterion can lead to unstable oxoammonium salts. Nitrogen dioxide (NO_2) has been used to make oxoammonium nitrate.[1] The most common counterions are Br^-, Cl^-, Br_3^-, ClO_4^-, BF_4^-, SbF_6^-, NO_3^-, and ClO_2^-. The only commercially available oxoammonium salt is Bobbitt and coworkers'[15] stable, non-hygroscopic *N*-acetyl-4-amino oxoammonium tetrafluoroborate (X^- = BF_4^- and R = NHAc). The perchlorate salt (X^- = ClO_4^-)[16] is no longer used, due to its detonation potential.[17]

Since oxoammonium salts are colored, many oxidations are monitored colorimetrically. The reaction mixture usually turns from a bright yellow slurry into a white slurry.[16] Another advantage of using stoichiometric oxoammonium salts is that there is no cooxidant which might decrease selectivity. Reactions in acid and base differ in their mechanisms and chemoselectivities. The rate of the oxidation increases with increasing pH of the reaction medium; thus most oxidations were carried out under basic conditions. Under strongly acidic conditions, oxidation is

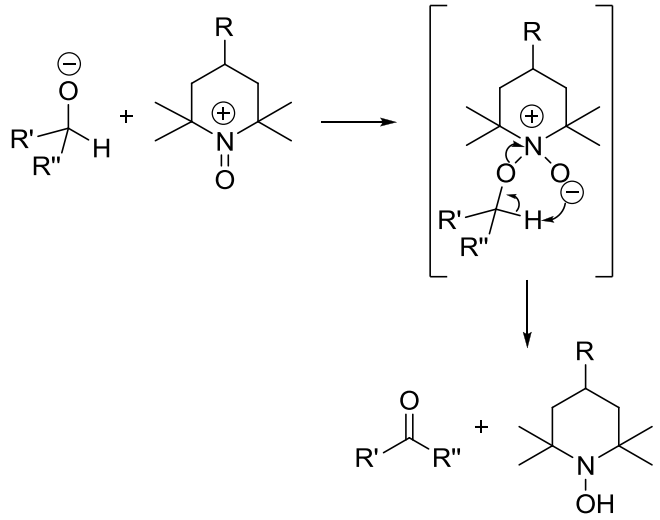
slow, and secondary alcohols are favored over primary. A mechanism involving hydride transfer to the electrophilic oxoammonium oxygen (**Scheme 1.2**) was first proposed by Golubev *et al*.[13,18] A kinetic isotope effect of k_H/k_D = 3.1 supports deprotonation as the rate-limiting step. A similar hydride transfer to an oxoammonium salt in the oxidative cleavage of benzyl alkyl ethers (*vide infra*) was reported recently by Bobbitt and coworkers.[19] Secondary alcohols react in preference to primary alcohols because of the weaker carbon-hydrogen bond strength, making secondary alcohols better hydride donors.



Scheme 1.2 Oxidation of alcohols with oxoammonium salts under acidic conditions

Under mildly acidic or basic conditions, oxidation is rapid, and primary alcohols react preferentially over secondary alcohols. The mechanism, originally proposed by Semmelhack *et al*.,[20] involves the nucleophilic attack of the alcoholate on the nitrogen of the oxoammonium salt, followed by intramolecular deprotonation in an oxa-Cope fragmentation (**Scheme 1.3**).[18, 20] The slower addition of more hindered secondary alcohols to the oxoammonium species explains the

preferential oxidation of primary alcohols. A kinetic isotope effect of k_H/k_D = 1.8 supports this mechanism.



Scheme 1.3 Oxidation of alcohols with oxoammonium salts under basic conditions

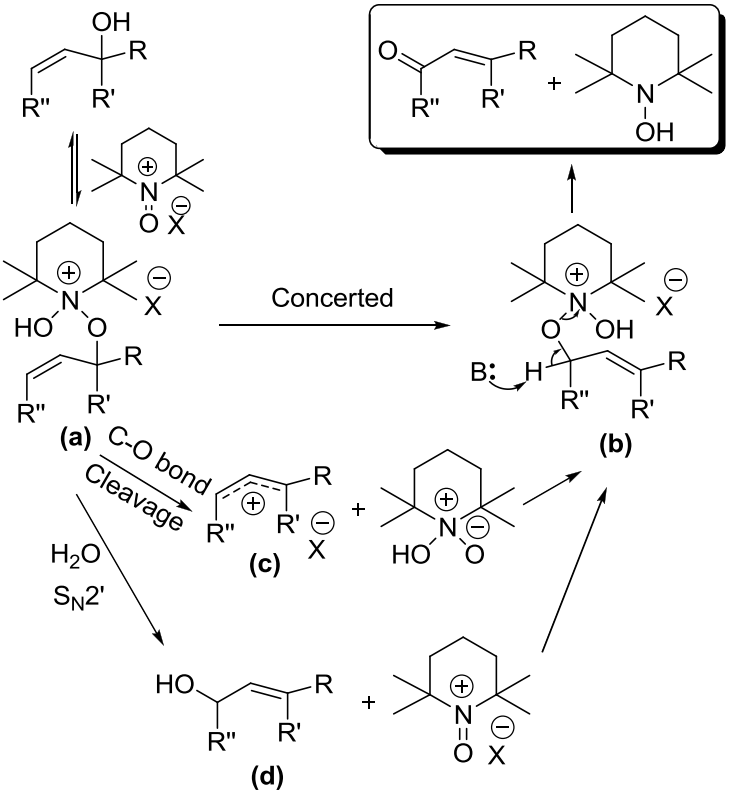
The oxidation of alcohols with oxoammonium salts has been reviewed by Bobbitt *et al*.[1,6] As an example, stoichiometric, *N*-acetyl-4-amino oxoammonium tetrafluoroborate has been used to oxidize unsaturated alcohols. In the synthesis of an insect pheromone, an ω-haloalkenol was oxidized in the presence of silica gel or pyridine in higher yield than with PCC.[21] However, alcohols bearing isolated dienes can suffer from acid catalyzed destruction of olefins in the presence of silica gel. The use of pyridine instead of silica gel circumvents this problem. Two equivalents of pyridine are required in the synproportionation reaction. The pyridine conditions allow oxidation of substrates bearing acid-sensitive protecting groups such as acetals

and silyl ethers. Alcohols containing a β-oxygen substituent do not undergo oxidation under mildly acidic conditions due to intramolecular hydrogen bonding.[16] However, they are oxidatively dimerized in the presence of pyridine to esters.[15] Tetraethylene glycol was oxidized and cyclized to a 12-membered ring lactone with oxoammonium salts supported on a polymer surface.[22] Stoichiometric oxoammonium salt has been utilized in the selective oxidation of monosaccharides under basic conditions.[23,24]

Iwabuchi and coworkers recently reported one pot oxidation of primary alcohols to the corresponding carboxylic acids using oxoammonium salts generated *in situ* from a unhindered class of nitroxides: 1-methyl-azaadamantane *N*-oxyl (1-Me-AZADO), in combination with $NaClO_2$.[25] The oxoammonium ion reacts with the alcohol to give an aldehyde, which then reacts with $NaClO_2$ to give the carboxylic acid product. These reactions conditions are notable in that the reaction medium is virtually bleach-free, as the destructive NaOCl byproduct is immediately consumed by the hydroxylamine to regenerate the oxoammonium ion. As a result, carboxylic acids are obtained in good yields without competing oxidation of electron-rich alkenes and aromatic rings. In contrast, the use of the more traditional "Merck method" employing TEMPO/NaOCl/$NaClO_2$ failed.[26]

Tertiary allylic alcohols undergo an oxidative rearrangement on treatment with oxoammonium salts.[27] Three possible mechanistic pathways have been

purposed (**Scheme 1.4**). In the first, addition of alcohol to the oxoammonium salt forms adduct **a**, which undergoes a concerted intramolecular rearrangement to form



Scheme 1.4 Three plausible reaction mechanisms for the oxidative rearrangement of tertiary allylic alcohols with oxoammonium salts

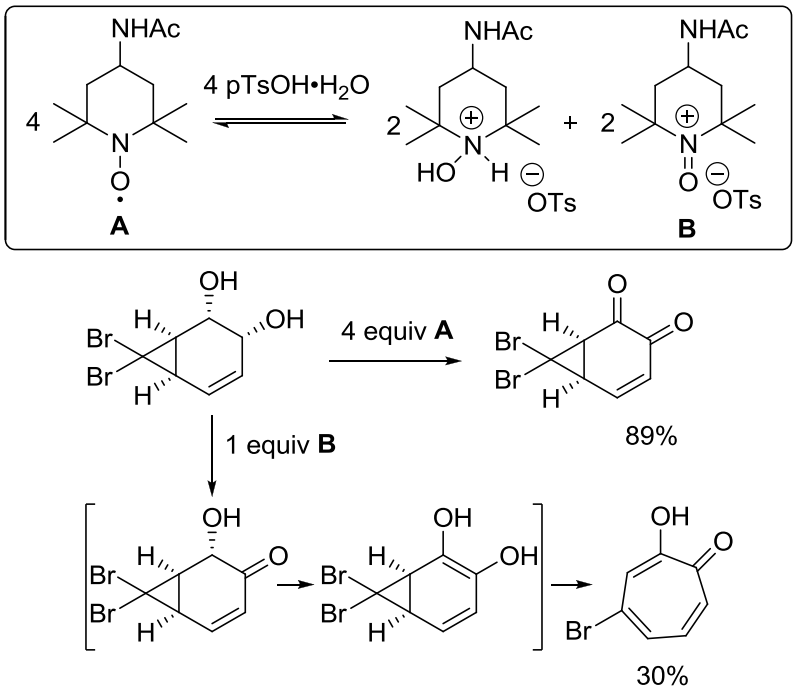
adduct **b**. Alternatively, adduct **b** can form via ionization of the allylic cation **c**. A third possibility is intermolecular S_N2' displacement by water to form allylic alcohol **d**, which can add to another oxoammonium to form intermediate **b**. Adduct **b** then fragments, presumably by deprotonation, to form the α,β-unsaturated ketone. Addition of water improves the yield in some cases. This reaction only works with

oxoammonium salts consisting of bulky and non-nucleophilic counter anions (BF_4^-, SbF_6^-).

1.2.2 In Situ Generation of Oxoammonium Salt by Acid-Catalyzed Disproportionation

Treatment of nitroxides with relatively strong acids such as peracids or *p*-toluenesulfonic acid facilitates disproportionation to form one oxoammonium salt *in situ* for every two equivalents of nitroxide. Since the medium must be below pH ≈ 2, this method is not suitable for acid labile substrates. When using *m*-chloroperbenzoic acid, hindered amines could be used directly, as they are oxidized by peracids to the nitroxides.[28,29] Bromide and chloride ions were found to be effective as cocatalysts. The disadvantages of using peracids are partial overoxidation of the aldehyde to the carboxylic acid, and competing epoxidation of double bonds. Baeyer-Villiger oxidation usually does not interfere since it is significantly slower than the nitroxide-mediated oxidation.[30] For example, two equivalents of nitroxide and two equivalents of *p*-toluenesulfonic acid were used to oxidize primary and secondary alcohols to aldehydes and ketones in high yield.[31] The resulting hydroxylamine salt can be recovered by filtration by using *N*-acetyl-4-amino-TEMPO instead of the parent TEMPO. This procedure was applied to the oxidation of open-chain and cyclic *vic*-diols to form *α*-dicarbonyls; C-C bond cleavage

was not observed.[32] In the example depicted in **Scheme 1.5**, the nitroxide-mediated oxidation gave the diketone in 89% yield, while use of the traditional Swern reagent produced only 68% yield. Interestingly, bromotopolone was the only product obtained when one equivalent of the preformed oxoammonium salt was used. This product arose via mono-oxidation to form an acyloin intermediate, which underwent enolization, electrocyclization, and finally dehydrobromination.



Scheme 1.5 Oxidation of 1,2-diol to α-diketone with oxoammonium salt generated *in situ* from acid-catalyzed disproportionation versus reaction with preformed oxoammonium salt

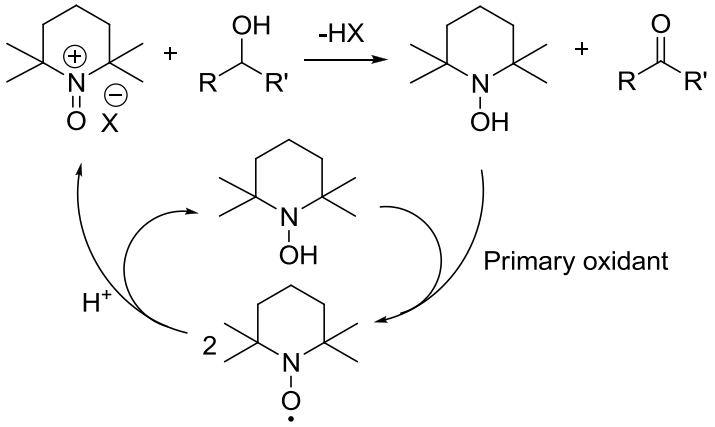
1.2.3 In Situ Regeneration of the Oxoammonium Salt by a Primary Oxidant

Although stoichiometric oxoammonium salts have been used successfully for the oxidation of alcohols, the ability to use the nitroxide in a catalytic fashion is more attractive. A variety of organic and inorganic primary oxidants have been used to oxidize the nitroxide, and to reoxidize the resulting hydroxylamine to the oxoammonium salt *in situ*. In the best cases, the stoichiometric oxidant is cheap (such as bleach), or even cleaner, such as O_2 or electrochemical anodic oxidation.

Conditions employing a stoichiometric cooxidant are generally milder than acid-catalyzed disproportionation. Since reactions are usually conducted under basic conditions, very high selectivity for primary alcohols in the presence of secondary alcohols is observed. Secondary alcohols can also be oxidized in good yields, but they need substantially longer reaction times. Despite the diversity of nitroxide radicals, TEMPO is frequently used, due to its cost and accessibility.

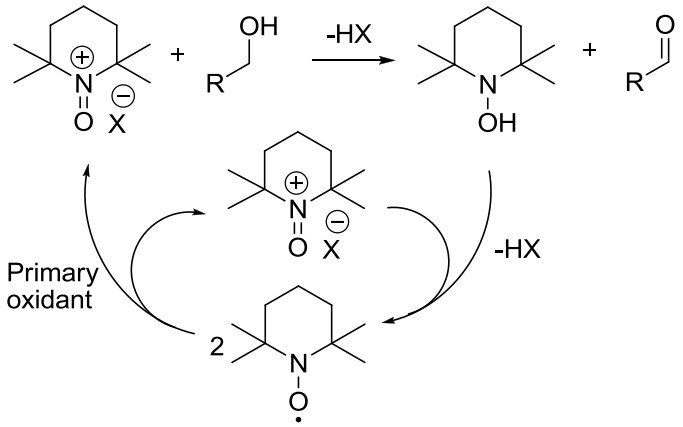
On the basis of the reversible acid-catalyzed disproportionation of nitroxides, general mechanisms of catalytic oxidation are described by two different scenarios, dictated as a function of pH.[3,33] Under highly acidic conditions (pH < 2) (**Scheme 1.6**), two nitroxides disproportionate to form one hydroxylamine and one oxoammonium salt. The latter oxidizes the alcohol; in doing so it is itself reduced to the

hydroxylamine. One-electron oxidation by the primary oxidant regenerates the nitroxide, which returns to the catalytic cycle.



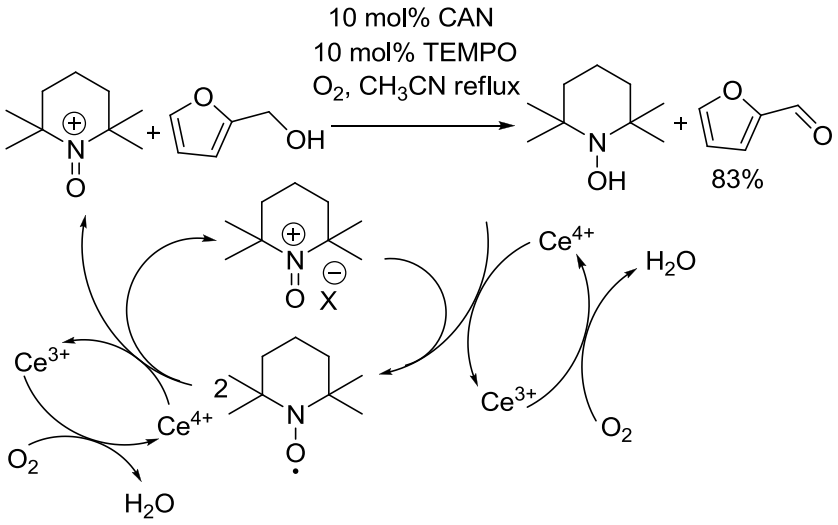
Scheme 1.6 Catalytic cycle of nitroxide-mediated alcohol oxidation under strongly acidic conditions

Alternatively, at higher pH (**Scheme 1.7**), the primary oxidant converts the nitroxide to the oxoammonium species, which is consumed by alcohol oxidation, reforming the hydroxylamine. The hydroxylamine can also react with an oxammonium ion to regenerate two nitroxide radicals in a synproportionation reaction.



Scheme 1.7 Catalytic cycle of nitroxide-mediated alcohol oxidation under weakly acidic and basic conditions

From both an economic and an environmental viewpoint, the use of "green" oxidants such as oxygen or hydrogen peroxide is ideal. The use of oxygen as a primary oxidant in conjunction with TEMPO and a transition metal catalyst (aerobic oxidation) has been investigated by a number of researchers (*vide supra*). Generally, the alcohol is oxidized by an oxoammonium cation, generating TEMPOH as a byproduct. The metal catalyst oxidizes the hydroxylamine to TEMPO, which is further oxidized by a second equivalent of metal catalyst back to the key oxoammonium salt. The reduced form of metal catalyst is reoxidized by oxygen as the primary oxidant. These conditions work with a broad range of alcohols. For example, an oxoammonium cation is formed by aerobic oxidation of TEMPO with the heteropoly acid $H_5PV_2Mo_{10}O_{40}$[34] or with ceric ammonium nitrate (CAN)[35] (**Scheme 1.8**).



Scheme 1.8 Catalytic cycle of CAN-mediated aerobic oxidation of alcohols

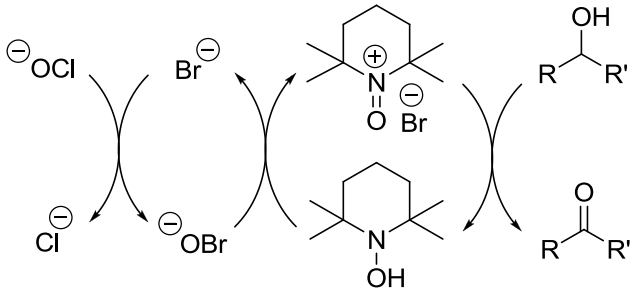
Alternatively, the oxoammonium salt can be generated via disproportionation of TEMPO in acetic acid under Minisci conditions,[12,36] in which Mn(II)-Co(II) or Mn(II)-Cu(II) nitrates are used to regenerate TEMPO from TEMPOH in the presence of oxygen. An easily recyclable reagent is the tetranitroxide derived from the commercially available hindered amine "CHIMASSORB® 966," which can be recovered by precipitation from organic solvents.[37]

The use of multicopper laccase enzymes has attracted much attention as a catalytic metal oxidant. These oxidase enzymes contain four copper centers per protein molecule. Laccase enzymes are secreted by white rot fungi to delignificate the lignocelluloses found in wood.[38] Galli and coworkers have reported a laccase/TEMPO system that catalyzes the oxidation of benzylic, allylic and aliphatic

alcohols, as well as benzylic amines.[39] However, 20-30 mol% of TEMPO is required, and this system is most effective with benzylic and allylic substrates. TEMPO outperforms other nitroxides examined in this oxidation.[40,41] The mechanistic details of this oxidation process are not completely clear, but it is assumed that electron transfer occurs from TEMPO to a Cu(II) in the laccase, forming an oxoammonium cation.[42-44] A kinetic isotope effect of k_H/k_D = 2.05 is consistent with an oxoammonium pathway.[41] Air is necessary to regenerate the Cu(II) species. The mechanistic pathway of the laccase/TEMPO system is different from other Cu/TEMPO systems (*vide infra*) due to the much higher redox potential of Cu(II) in laccase. It has been shown that laccase/TEMPO can catalyze the aerobic oxidation of primary alcohols in carbohydrates to form polycarboxylic acids.[33] The biodegradable carboxystarch product is an excellent water absorbent, with potential applications for use in diapers. However, obstacles towards large scale manufacture include the high cost and the instability of the enzyme.

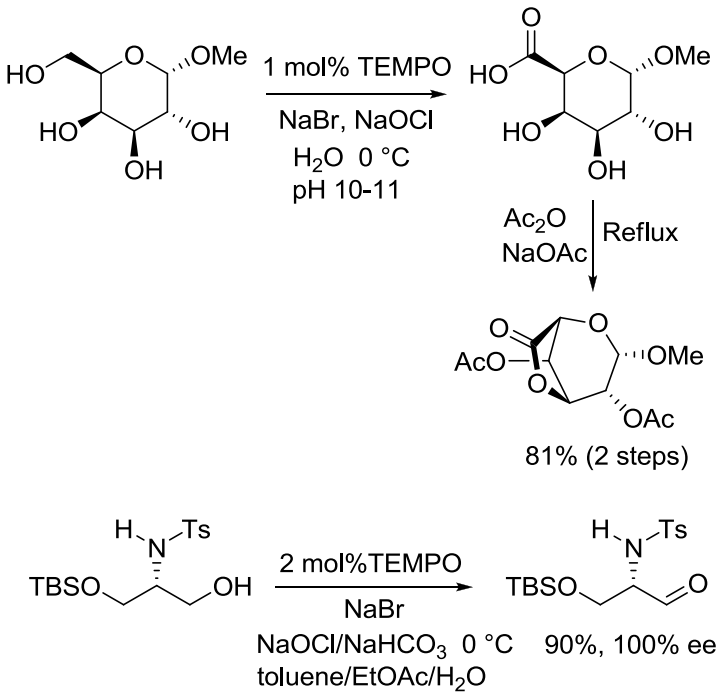
Anelli *et al*.[45,46] have developed a popular protocol that utilizes household bleach (sodium hypochlorite) as the stoichiometric oxidant, and requires only 1 mol% of the nitroxide. This oxidation uses mild biphasic conditions (CH_2Cl_2/H_2O, pH = 8.6-9.5); addition of bromide ion as a cocatalyst provides aldehydes in high yields with reaction times of only minutes. Bromide is oxidized by bleach to form hypobromite (a more reactive oxidant than hypochlorite) for regeneration of the

oxoammonium salt (**Scheme 1.9**). Oxidation of secondary alcohols requires slightly longer reaction times. Overoxidation of aldehydes to carboxylic acids resulted on



Scheme 1.9 Anelli oxidation of alcohols with TEMPO/NaOCl/KBr

addition of a phase transfer reagent. Carboxylic acids were obtained cleanly using sodium chlorite ($NaClO_2$) as the terminal oxidant with catalytic amounts of TEMPO and bleach in aqueous acetonitrile (Merck's method).[26,47,48] The oxoammonium salt, resulting from the combination of TEMPO and bleach, oxidizes the alcohol to the corresponding aldehyde. The hydrated hemiacetal then reacts with sodium chlorite to form the carboxylic acid. Anelli conditions have been utilized for the selective oxidation of monosaccharides[49-51] (**Scheme 1.10**), disaccharides,[52] oligosaccharides,[53] and polysaccharides[33,54-58] to their corresponding carboxylic acids. These reaction conditions are mild enough that epimerization does not occur with optically pure α-amino and α-hydroxy aldehydes (**Scheme 1.10**).[59,60] Recently, TEMPO-catalyzed oxidation with bleach was performed in a spinning tube-in-tube

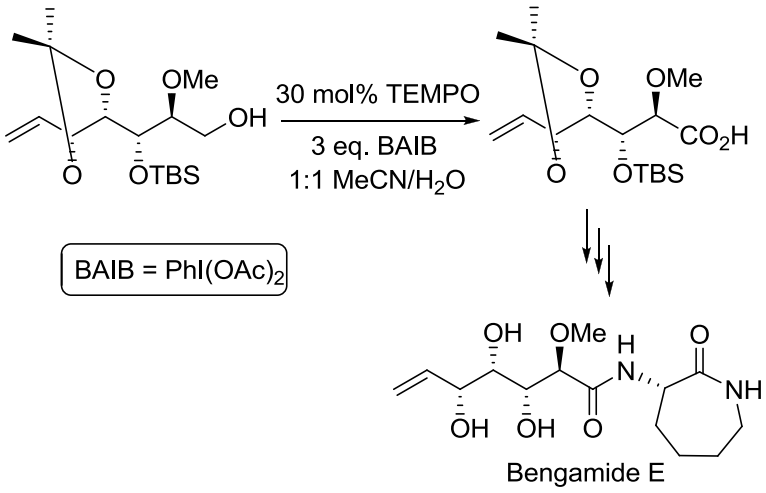


Scheme 1.10 Anelli oxidation of methyl α-D-galactopyranoside[137] and *N*-tosyl-α-amino alcohol[146]

reactor,[61] eliminating the need for slow addition of bleach to control the exothermic reaction. The rapid mixing and efficient heat transfer resulted in increased yields and enhanced reaction rates.

Although the Anelli protocol is widely utilized, it is not waste-free: the use of bleach produces one equivalent of sodium chloride for every molecule of alcohol oxidized. Chlorinated byproducts are sometimes formed. Alternative cooxidants include iodine-based oxidants, such as [bis(acetoxy)iodo]benzene ($PhI(OAc)_2$, BAIB),[62] iodine (I_2),[63] periodic acid (H_5IO_6),[64] iodine pentoxide (I_2O_5),[65] sodium

periodate ($NaIO_4$),[66] iodobenzene dichloride ($PhICl_2$),[67] and 1-chloro-1,2-benziodoxol-3(1*H*)-one.[68] Other oxidants examined include *N*-chlorosuccinimide (NCS),[69] Oxone®,[70] hydrogen peroxide,[71] sodium bromite ($NaBrO_2$),[72] and pyridine/HBr_3.[73,74] Trichloroisocyanuric acid (TCCA) can also be used as a hypochlorite equivalent.[75,76] Margarita's TEMPO-mediated alcohol oxidation protocol using BAIB as the terminal oxidant[62] is particularly good at avoiding epimerization with sensitive substrates. Thus it has become very popular, as exemplified by its use in the total syntheses of natural products such as pteridic acid A,[77] guanacasterpene A,[78] and bengamide E.[79] In the case of bengamide E, an antitumor natural product of marine origin, oxidation of an alcohol to the carboxylic acid was successful in the presence of water (**Scheme 1.11**).



Scheme 1.11 TEMPO/BAIB oxidation of a primary alcohol to the carboxylic acid in the total synthesis of bengamide E

Both the Anelli[46] and Margarita[80] conditions oxidize 1,4- and 1,5-diols to the corresponding γ- and δ-lactones, respectively, via a cyclic hemiacetal intermediate. Both conditions also exhibit high chemoselectivity for oxidation of primary alcohols. Aerobic oxidation of benzylic alcohols has been demonstrated with catalytic amounts of TEMPO/BAIB/KNO_2 under solvent-free conditions.[81] Immobilization of BAIB on polystyrene (PS) allows for the recycling of this catalyst. An oxidative rearrangement of tertiary allylic alcohols with catalytic TEMPO failed using bleach, BAIB, or Oxone® as the stoichiometric oxidant. However, it worked well when $NaIO_4$ on silica gel[82] or PhIO in conjunction with a Lewis acid[83,84] were employed as terminal oxidants. TEMPO and related derivatives are more effective catalysts than other nitroxides.[85] Recently, unhindered 1-methyl azaadamanthane *N*-oxyl (1-Me AZADO),[7,86,87] 5-fluoro azaadamanthane *N*-oxyl (5-F-AZADO),[88] 9-azanoradamantane *N*-Oxyl (Nor-AZADO),[89] and several azabicyclo *N*-oxyls,[90,91] such as 9-azabicyclo[3.3.1]nonane-*N*-oxyl (ABNO)[91] (**Figure 1.1**), have been shown to exhibit even greater activity than TEMPO under both Anelli, Margarita and electrochemical oxidation conditions.

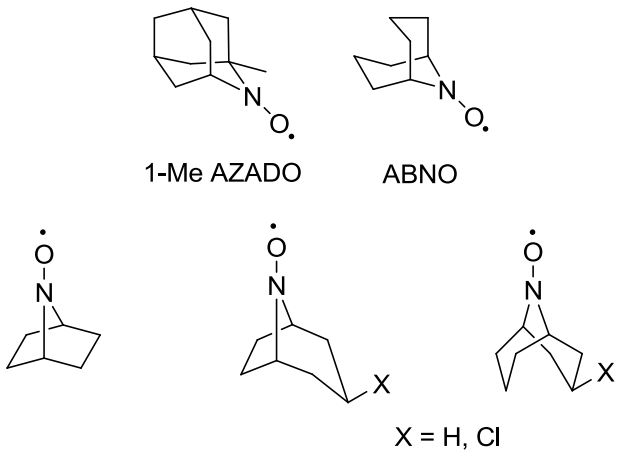
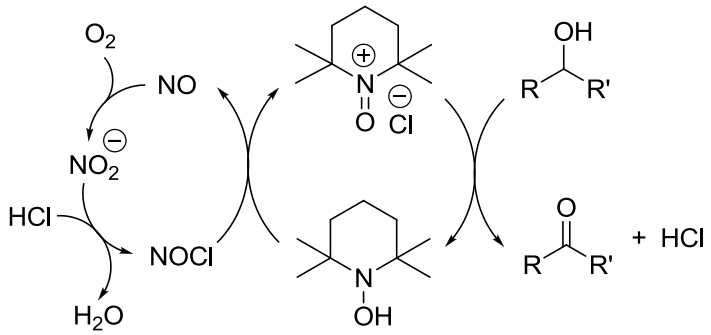


Figure 1.1 Iwabuchi's sterically unhindered 1-methyl azaadamanthane *N*-oxyl (1-Me AZADO) and Onomura's azabicyclo *N*-oxyl nitroxides effective in catalytic oxidations

Hu and coworkers reported the first transition metal-free aerobic alcohol oxidations with catalytic TEMPO using $Br_2/NaNO_2/O_2$.[92] They demonstrated that HCl[93] or 1,3-dibromo-5,5-dimethylhydantoin[94] could serve the same function as Br_2. The nitric oxide precursor $NaNO_2$ can also be replaced by *tert*-butyl nitrite[95,96] or hydroxylamine.[97] Recently, Yang and coworkers have shown that both NO and Br^- can be generated *in situ* by reaction of $NH_2OH{\bullet}HCl$ and $KBrO_3$.[98] The proposed mechanism for alcohol oxidations using catalytic amounts of TEMPO/$NaNO_2$/HCl and air as the ultimate oxidant is described in **Scheme 1.12**. The alcohol is oxidized by the oxoammonium salt, which is regenerated by oxidation of TEMPOH with NOCl. NOCl is formed by reaction of HCl and NO_2^-, which is generated by air oxidation of NO. Water is a byproduct of this reaction cycle.



Scheme 1.12 Mechanism of aerobic transition metal-free oxidation with TEMPO/HCl/$NaNO_2$

Although only catalytic amounts (often 1 mol%) of nitroxide are commonly used in alcohol oxidations, the ability to efficiently isolate and recycle the catalyst is also important. Hence many groups have designed variants on immobilized nitroxides anchored to solid supports, such as silica[99-101] or mesoporous silica MCM-41.[102] Other strategies include entrapment in a silica sol-gel,[103-105] or coupling the nitroxide to functionalized polymers.[106, 107] Silica-supported TEMPO catalysts have several advantages: they are easily isolated by filtration, a high catalyst activity can be realized due to the high surface area, the nitroxides can be cleanly regenerated electrochemically, and some are commercially available (for example, Silia*Cat*®[108] (**Figure 1.2**) and FibreCat®[109]). The heterogeneous catalysts are often less active than the homogeneous catalysts.[110] Most of TEMPO-polymer conjugates are soluble in selected organic solvents; the catalyst is recovered by precipitation induced by changing the solvent system,[111] or by dialysis.[112] PEG-supported TEMPO (**Figure**

1.2)[113] is the most popular homogeneous catalyst for use under Anelli,[107,114-116] Minisci[117] and aerobic copper-mediated conditions.[113,118] The recyclable polyamine-immobilized piperidinyl oxyl (PIPO) [110,119] (**Figure 1.2**) prepared from the commercially available antioxidant and light stabilizer CHIMASSORB® 944, in combination with bleach exhibited higher activity (per nitroxyl group) than TEMPO, silica- and MCM-41-supported TEMPO.

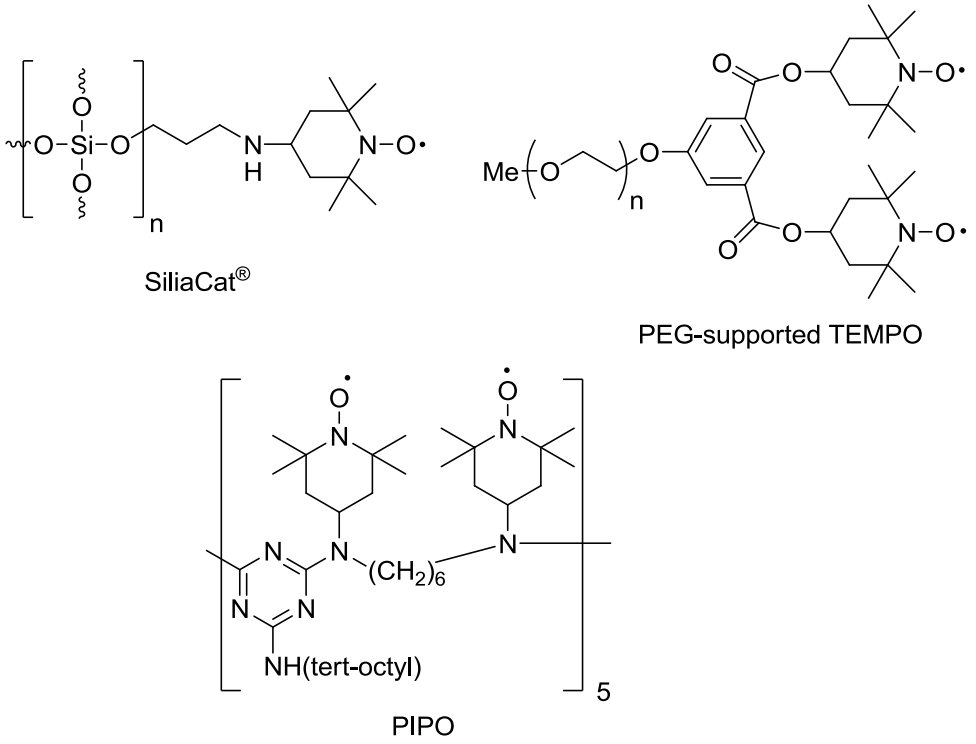
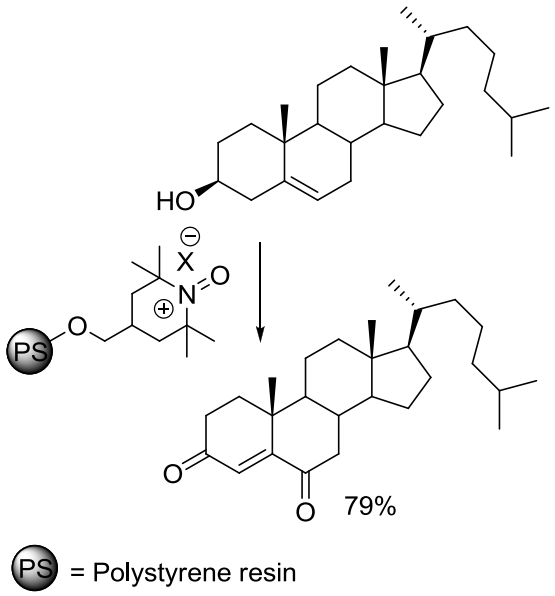


Figure 1.2 Examples of silica- and polymer-supported TEMPO reagents

There are several TEMPO-polymer conjugates that behave as insoluble heterogeneous catalysts, such as PS-based TEMPO,[106,112,120,121] TEMPO-

functionalized PS encapsulated in polyurea microcapsules.[122] Recently Studer[123] and coworkers reported TEMPO-poly(amidoamine) dendrimers (PAMAM) conjugates coated inside polyparaxylylene nanotubes for benzylic alcohol oxidations under Anelli conditions. As shown in **Scheme 1.13**, cholesterol was oxidized by a preformed oxoammonium PS resin to form an enolizable ketone intermediate, which was further converted to the dione.[22] Tanaka and coworkers have regenerated polymeric oxoammonium salts by electrochemistry.[124] Immobilized cooxidants such as poly[4-(diacetoxyiodo)styrene,[125-127] polymer-supported bisacetoxybromate(I) anion,[128,129] and polymer-supported hypochlorite resins[130,131] have been developed.



Scheme 1.13 Oxidation of cholesterol by a polystyrene oxoammonium resin

Instead of attaching the nitroxide to a solid support, monomeric TEMPO tethered to a charged imidazolium species (**Figure 1.3**)[132] can be isolated by extraction into an ionic liquid, leaving the oxidized product in the organic layer.[133, 134] Imidazolium salts have also been tethered to 2,2′-bipyridine (bipy) ligands for use

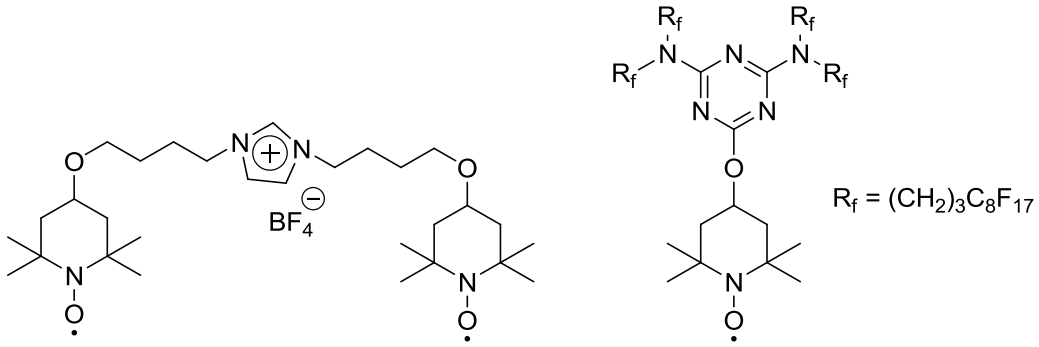


Figure 1.3 Examples of TEMPO derivatives bearing imidazolium salt and fluorous tags

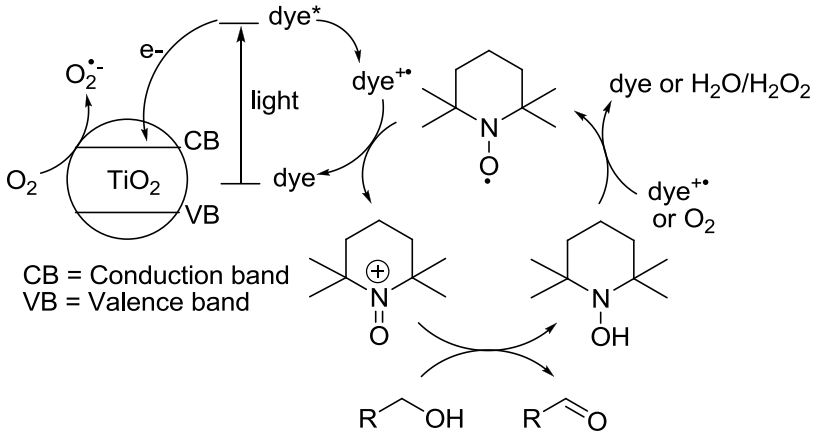
in TEMPO/Cu oxidations.[135] The nitroxide *N*-acetyl-4-amino-TEMPO was found to be soluble in an ionic liquid, but not in ether, allowing it to be recycled thrice without loss of activity.[136] Perfluoroalkyl chains impart solubility in fluorous solvents (**Figure 1.3**).[137] Several fluorous-tagged TEMPO derivatives have been applied successfully under Anelli,[137-140] Margarita[137] and Minisci[139, 141] oxidation conditions. This strategy has also been used to append perfluoroalkyl chains onto 2,2′-bipy ligands for TEMPO/Cu mediated alcohol oxidations, allowing the Cu-ligand complexes to be reused several times.[141-144] Recently, TEMPO was immobilized on saponite, allowing

isolation of the nitroxide by filtration,[145] and on graphene-coated cobalt nanoparticles,[146] which can be separated from solution by magnetic decantation.

As an alternative to chemical oxidants, electrochemistry has also been utilized to reoxidize nitroxides in alcohol oxidations. Cyclic voltammetry has been used to measure the formation of oxoammonium salts from nitroxides: the lower the oxidation potential of the nitroxide, the more effective the nitroxide is at mediating alcohol oxidation.[85] Oxidation potentials are also a function of solvent polarity; polar solvents enhance the oxidation efficiency.[147] Electrooxidations have been conducted in dichloromethane, acetonitrile, biphasic medium or water in a divided cell[148,149] as well as in undivided cells.[150] Ionic, water soluble[151,152] or polymer immobilized[124,153,154] nitroxides have been used in electrooxidation of alcohols. Nitroxides have been immobilized on the electrodes to simplify the work-up.[155-157] The popular nitroxide SG1, commercially available from Arkema, was successfully used in electrooxidation of 4-methylbenzyl alcohol, and showed smoother electron transfer on the electrode compared to TEMPO.[158] TEMPO electrooxidation has been performed in an ionic liquid.[159] Schafer and Bashiardes have demonstrated the nitroxide-catalyzed oxidation of mono-, di-, oligo- and polysaccharides electrochemically.[160,24,150,161]

Recently, an interesting method to regenerate an oxoammonium cation from the nitroxide using visible light has been reported (**Scheme 1.14**).[162] This system

consists of the dye Alizarin as a sensitizer, TiO_2 as an electron acceptor, and TEMPO as a cocatalyst in benzotrifluoride as solvent. Under irradiation with visible light (λ > 450 nm), an electron from the excited state of the dye is transferred to the conduction band of TiO_2; the dye radical oxidizes TEMPO to the oxoammonium cation. After alcohol oxidations, TEMPO is then regenerated by either oxygen or the dye radical cation. In a similar system, porphyrin was utilized as the photosensitizer and quinone as the electron acceptor.[163]

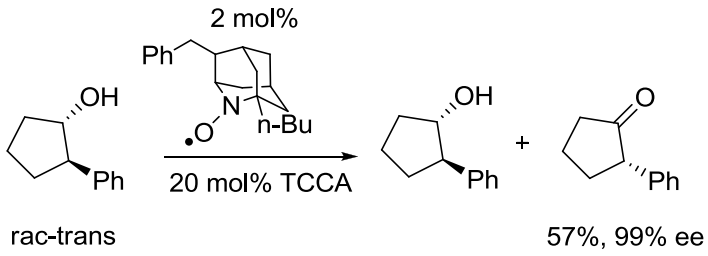


Scheme 1.14 Mechanism for the visible light-induced aerobic oxidation of primary alcohols in a coupled photocatalytic dye-sensitized TiO_2/TEMPO system

1.3 Kinetic Resolution and Desymmetrization

Optically pure nitroxides[164] have been used as oxidants to carry out kinetic resolution of racemic substrates, and desymmetrization of *meso* substrates. The selectivity value *S* is often used to combine both %ee (enantiomeric excess) and

conversion into a measure of overall effectiveness in kinetic resolution. Bobbitt and coworkers reported the first examples of kinetic resolution of alcohols with a chiral nitroxide using 4-NHAc SPIROXYL,[165,166] including the asymmetric lactonization of diols.[165, 167] Using an axially chiral nitroxide[168] or nitroxyl peptide (TOAC)[169] under Anelli conditions, moderate selectivities in the kinetic resolution of secondary alcohols was achieved (*S* = 3.9-7.1 and *S* = 2.3, respectively). Electrochemical oxidation with the axially chiral nitroxide provided *S* values as high as 20.[170] Several chiral bridgehead nitroxides were examined; however, most of them were unstable under oxidation, resulting in poor *S*-values.[171] Recently, excellent enantioselectivities (*S* values up to 82) using the chiral azaadamantane nitroxide AZADO in combination with TCCA has been reported (**Scheme 1.15**).[172,173]



Scheme 1.15 Enantioselective organocatalytic oxidative kinetic resolution of secondary alcohols using optically AZADO

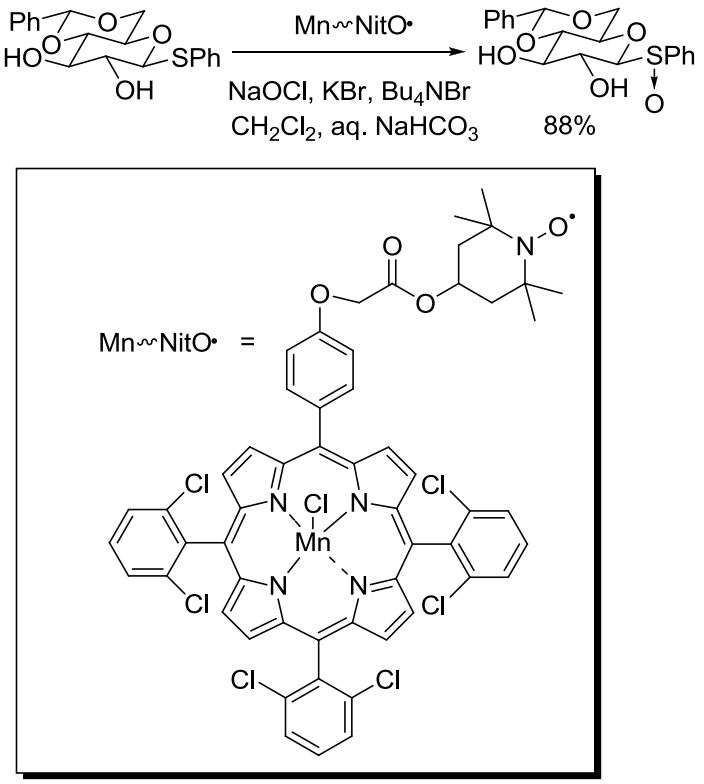
(-)-Sparteine has been used as a chiral base with TEMPO-modified electrodes[167,174,175] and as a ligand with copper[161] in enantioselective oxidations. A chiral copper complex, prepared from $Cu(OTf)_2$ and (*R*)-BINAM was used with TEMPO in the oxidative kinetic resolution of racemic amino alcohols,[176] benzylic

alcohols, and benzoins.[177] Kinetic resolution of secondary amines[178] and oxazolidines[179] have also been reported. Optically active acyl and diacyl (phthalimido) nitroxides have been used in both oxidative kinetic resolution and desymmetrization;[180,181] however, the mechanism does not involve an oxoammonium salt, but rather hydrogen abstraction (*vide infra*).

1.4 Other Oxidations Mediated by Oxoammonium Salts

1.4.1 Oxidation of Sulfides to Sulfoxides, and Thiols to Disulfides

A variety of sulfides can be oxidized selectively to sulfoxides in nitroxide-mediated reactions under Anelli[182-185] or copper-mediated[186] conditions. For example, TEMPO-linked Fe- and Mn-metalloporphyrins were used as a catalyst to oxidize sulfides to the corresponding sulfoxides without overoxidation to the sulfone.[185] The glycosyl sulfide in **Scheme 1.16** was chemoselectively oxidized in the presence of two hydroxyl groups under Anelli conditions. The electrochemical oxidation of thiols to disulfides has been accomplished with a TEMPO-modified electrode.[187]

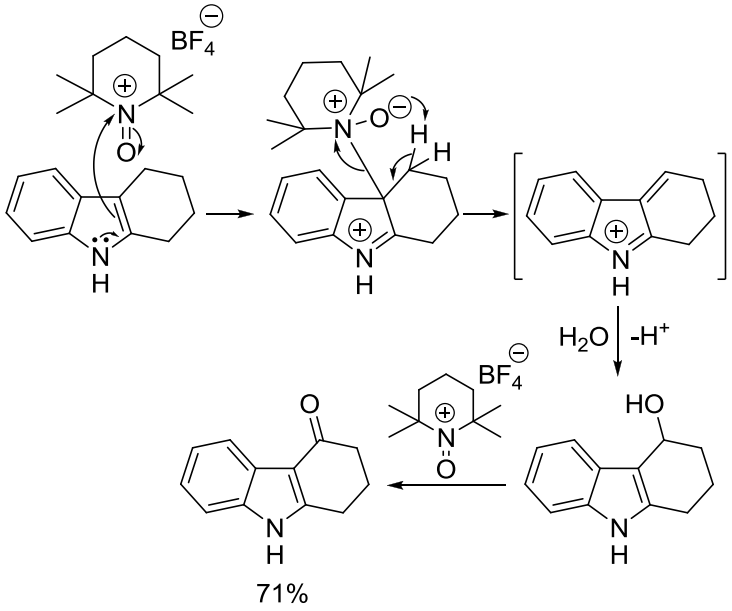


Scheme 1.16 Oxidation of a glycosyl sulfide to the corresponding sulfoxide with a TEMPO-linked Mn-metalloporphyrin under Anelli conditions

1.4.2 Allylic Oxidations

Trisubstituted alkenes can undergo allylic oxidation with oxoammonium salts to form alkoxyamines: Bobbitt and coworkers have suggested an ene-type mechanism.[188] Similar examples include the allylic oxidation of dienes, activated alkenes[189] and tetrahydrocarbazole[190] to form the corresponding conjugated ketones in excellent yields. For example, 1,2,3,4-tetahydrocarbazole (**Scheme 1.17**) was oxidized to the ketone in 71% yield. The proposed mechanism involves

nucleophilic attack by the indole on the oxoammonium salt, followed by intramolecular elimination to give the unsaturated iminium cation. Conjugate addition of water forms the 4-hydroxytetrahydrocarbazole, which is subsequently oxidized to the ketone product.

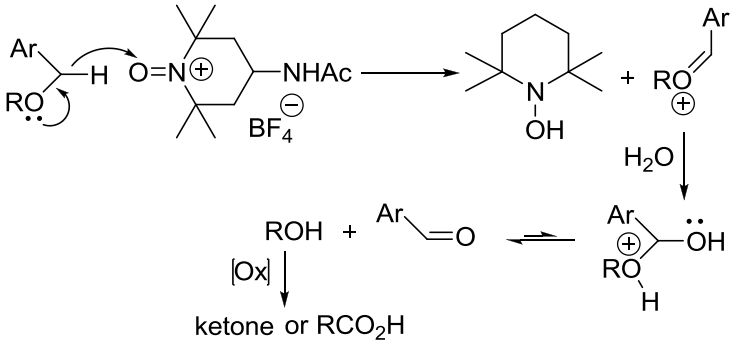


Scheme 1.17 Allylic oxidation of 1,2,3,4-tetahydrocarbazole to 4-keto-1,2,3,4-tetahydrocarbazole by two equivalents of an oxoammonium salt

1.4.3 Oxidative Cleavage of Benzyl Alkyl Ethers

Oxidative cleavage of benzyl alkyl ethers occurs upon treatment with oxoammonium salts bearing non-nucleophilic counterions such as BF_4^- (**Scheme 1.18**). The mechanism occurs via benzylic hydride transfer to the electrophilic oxygen of the oxoammonium salt; hydrolysis of the oxygen-stabilized benzylic cation

forms an aromatic aldehyde and an aliphatic alcohol.[19] The aliphatic alcohol is further oxidized to the corresponding ketone or carboxylic acid. In contrast, using a nucleophilic bromide counterion to the oxoammonium cation, anhydrous conditions result in the formation of an aromatic aldehyde and an alkyl bromide.[191,192]

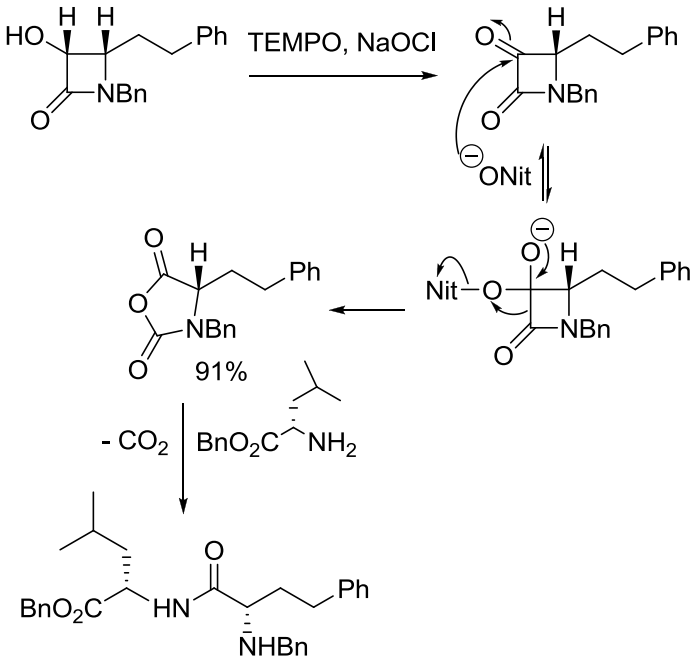


Scheme 1.18 Oxidative cleavage of a benzylic ether using a typical oxoammonium salt

1.4.4 Baeyer-Villager Reactions

Baeyer-Villiger reactions of *α*-hydroxy ketones can be carried out by nitroxides plus an oxidant, such as bleach.[193-195] In the first step, the *α*-hydroxy ketone is oxidized by the oxoammonium salt to the corresponding *α*-diketone, which undergoes further oxidation to form the anhydride. The mechanism for the oxidative ring enlargement is not clear, but may occur by nucleophilic addition of the hydroxyamine anion to one of the carbonyls, followed by ring expansion with loss of the hindered aminyl anion. For example, peptides can be prepared from *β*-lactams

via nitroxide-mediated Baeyer-Villiger reaction under Anelli conditions, followed by nucleophilic amidolysis with an amino acid (**Scheme 1.19**).[195]



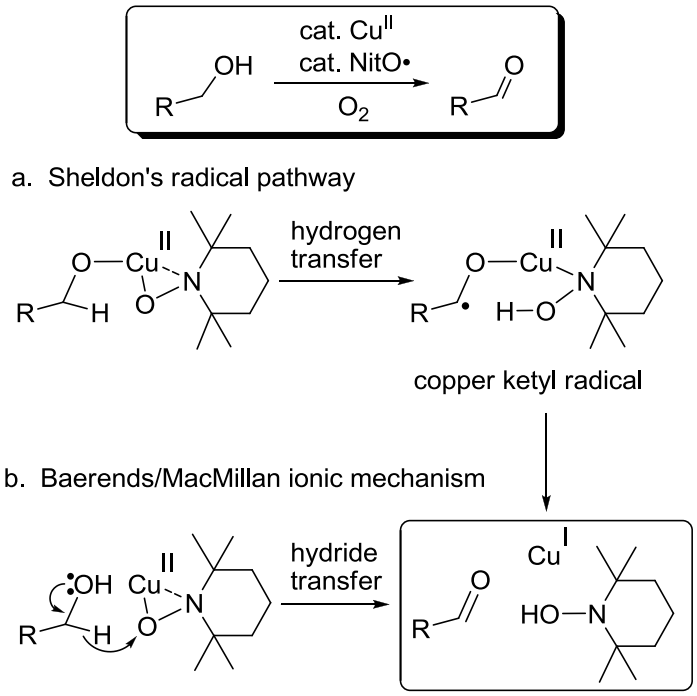
Scheme 1.19 Synthesis of a peptide via Baeyer-Villager reaction of a β-lactam with TEMPO and bleach

1.5 Oxidations via Hydrogen Abstraction

1.5.1 Copper, Ruthenium and Iron-Catalyzed Aerobic Oxidations

A number of reports utilize copper, ruthenium or iron with a nitroxide and oxygen to oxidize alcohols to carbonyl compounds. This literature has been reviewed by Sheldon and Arends[196,197] and Sheldon *et al*.[5] Copper cocatalysts are the most extensively investigated among the transition metals in these aerobic nitroxide

oxidations. Semmelhack *et al*. proposed that benzylic and allylic alcohols were oxidized by CuCl/TEMPO via the oxoammonium salt.[20,198] Evidence against this pathway includes the lower reaction rates of aliphatic and alicyclic alcohols compared to benzylic and allylic substrates. This chemoselectivity is inconsistent with a mechanism involving an oxoammonium cation, whose reactivity is broad in scope. Stoichiometric experiments under anaerobic conditions support a formation of an electrophilic Cu/TEMPO complex rather than an oxoammonium species.[199] Additional evidence for an alternative reaction pathway includes kinetic isotope effects and Hammett correlation studies. The primary kinetic isotope effect for the CuCl/TEMPO catalyzed aerobic oxidation (k_H/k_D = 5.42) compares well with those observed with other metal-centered dehydrogenations of alcohols, such as a Ru/TEMPO system,[200] galactose oxidase,[201] and a biomimetic copper complex.[202] In contrast, the kinetic isotope effects observed in stoichiometric oxoammonium cation oxidations are much smaller (k_H/k_D = 1.7-2.3).[20] The Hammett ρ value for the CuCl/TEMPO system also compares well with that of a galactose oxidase mimic. Sheldon and coworkers[203,204] have proposed an intramolecular hydrogen atom abstraction as the key step in the Cu/TEMPO catalytic aerobic cycle; however calculations support a possible ionic hydride transfer mechanism[205,206] (**Scheme 1.20**). After alcohol oxidation, the resulting Cu(I) and TEMPOH are reoxidized by O_2 to Cu(II) and TEMPO, respectively.

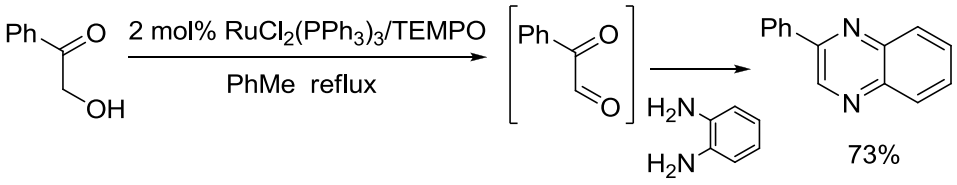


Scheme 1.20 Two proposed mechanisms for Cu/TEMPO cocatalyzed aerobic oxidation of alcohols: (a) via an intramolecular hydrogen atom transfer and (b) via hydride transfer to an electrophilic Cu/TEMPO complex

Several ligands, such as 2,2′-bipy,[203,204,207] 1,10-phenanthroline (phen),[208] pyrazole derivatives,[209] and DABCO,[210] as well as bases such as *t*-BuOK,[203,204] NaOH,[203,208] KOH,[203,207] and DBU[207] have been utilized in copper-complex mediated aerobic oxidation of alcohols. Under one set of conditions, no base was required, and the Cu(II) complex could be reused three times without loss of reactivity.[211] The use of a dinuclear Cu(II) complex was reported, but only works with primary benzylic alcohols.[289] Recently, a Cu(II) complex immobilized on a silica support was utilized in supercritical carbon dioxide ($scCO_2$).[212] These copper-mediated oxidations are

selective, giving very good yields with primary benzylic and allylic alcohols, and in a few cases with secondary benzylic alcohols.[208] There are a few reports in which primary aliphatic alcohols can be used.[203,211] Recently, TEMPO/Cu has been employed in the aerobic oxidative rearrangement of a tertiary allylic alcohol.[213]

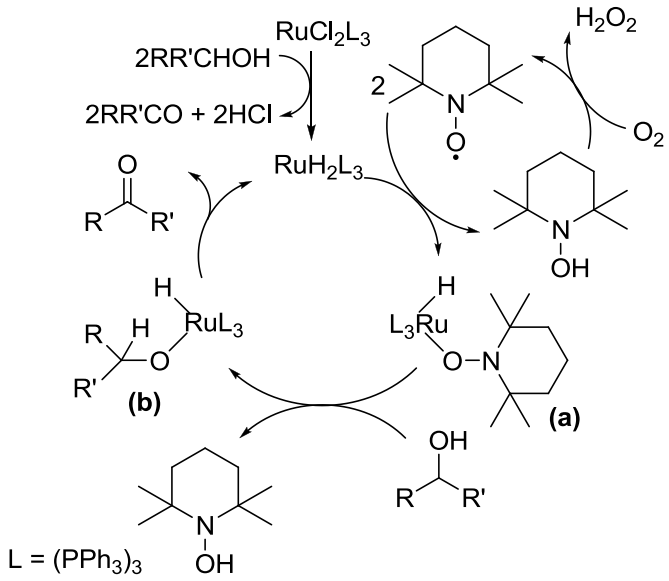
In contrast to copper, catalytic TEMPO/$RuCl_2PPh_3$ at 100 °C is effective for the aerobic oxidation of a broad range of alcohols, including aliphatic alcohols.[200,214] The autooxidation of aldehydes to carboxylic acids under these conditions is completely suppressed by TEMPO, which acts as a carbon free radical scavenger. However, alcohols containing heteroatoms such as nitrogen cannot be oxidized by this system, as they deactivate the ruthenium catalyst by coordination as ligands.[5] This aerobic Ru/TEMPO system was shown to convert *α*-hydroxy ketones into 1,2-diketones, which were trapped *in situ* with aromatic 1,2-diamines to form quinoxalines (**Scheme 1.21**).[215]



Scheme 1.21 Oxidation of *α*-hydroxy ketones with Ru/TEMPO, followed by trapping with 1,2-diamines to form quinoxalines

From mechanistic studies on the Ru/TEMPO system, $RuCl_2(PPh_3)_3$ gets reduced to $RuH_2(PPh_3)_3$, possibly by oxidation of a small amount of the alcohol

(**Scheme 1.22**).[5] Reaction with two equivalents of TEMPO forms TEMPOH and the ruthenium alkoxyamine complex **a**. The piperidinyloxy ligand in complex **a** is displaced by alcohol to form another equivalent of TEMPOH and complex **b**, which undergoes the key β-hydride elimination, to afford the carbonyl product and regenerating the RuH_2PPh_3 catalyst.



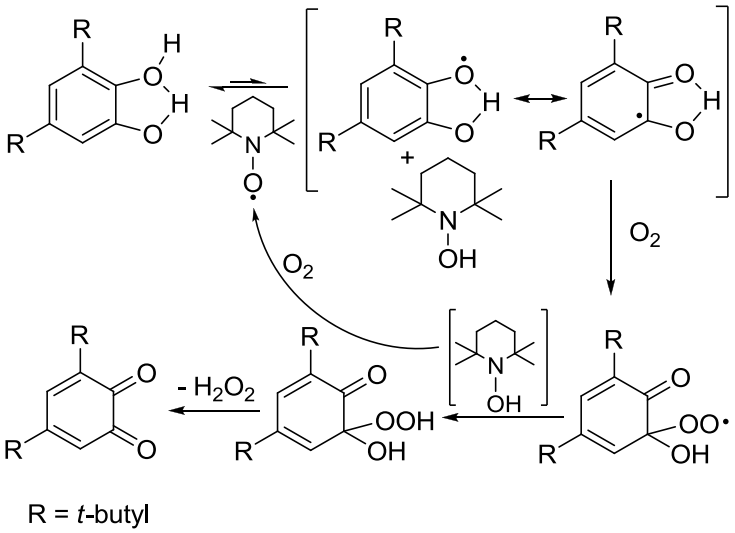
Scheme 1.22 Proposed mechanism for the Ru/TEMPO catalyzed aerobic oxidation of alcohols

Interestingly, Liang *et al*. have investigated the use of an inexpensive and environmentally friendly TEMPO/$FeCl_3$/$NaNO_2$ system[216,217] to oxidize a broad range of alcohols including aliphatic alcohols under ambient conditions, in contrast to the TEMPO/$RuCl_2PPh_3$ system which requires heating to 100 °C.[200] Further optimization

of these reaction conditions has been explored by several groups.[217,218] An iron-activated electrophilic TEMPO complex involving a hydrogen abstraction pathway reminiscent of the Cu(II)/TEMPO system is likely. The catalytic cycle involves the oxidation of Fe(II) to Fe(III) by NO_2, and the oxidation of TEMPOH to TEMPO by Fe(III). The stoichiometric oxidant, molecular oxygen, regenerates the NO_2.

1.5.2 TEMPO Reactions with Phenols and Catechols

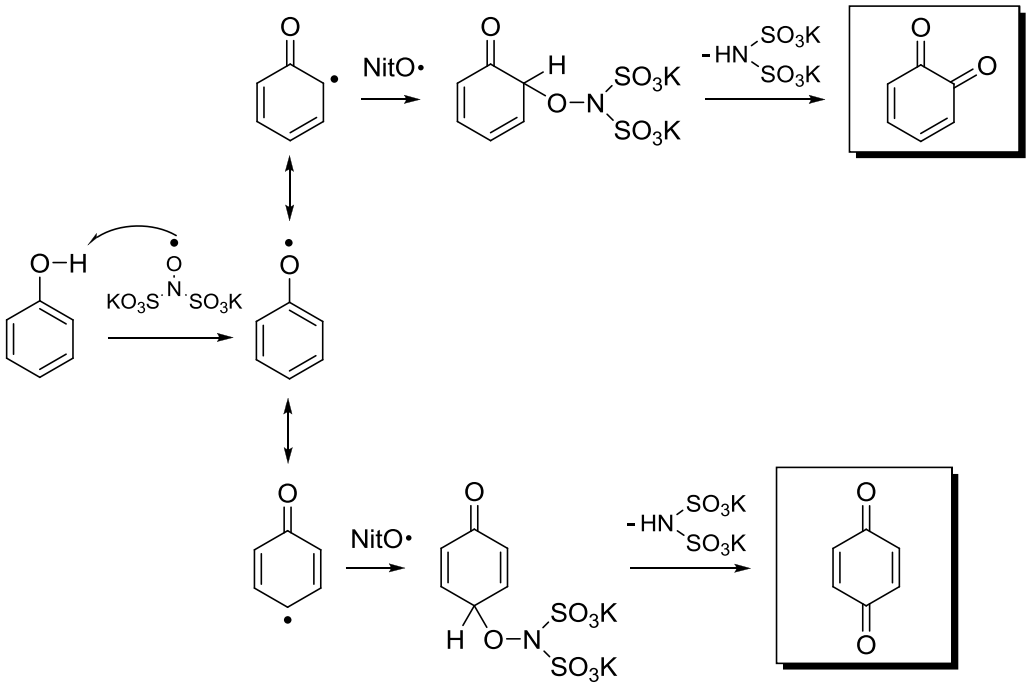
TEMPO and derivatives oxidize phenols and catechols, such as 3,5-di-*tert*-butylcatechol,[219] 2-aminophenol,[220] L-tyrosine[221] and *o*-phenylenediamine[222] via hydrogen atom abstraction under aerobic conditions. A proposed mechanism for the oxidation of 3,5-di-*tert*-butylcatechol is shown in **Scheme 1.23**. Semiquinone radical, produced by hydrogen abstraction by TEMPO of the very activated catechol OH, is readily trapped by molecular oxygen to give a peroxyl radical. This peroxyl radical in turn abstracts hydrogen atom back from TEMPOH to regenerate TEMPO. The hydroperoxide intermediate breaks down to form quinone and hydrogen peroxide.



Scheme 1.23 Proposed mechanism of aerobic TEMPO-catalyzed 3,5-di-*tert*-butylcatechol oxidation

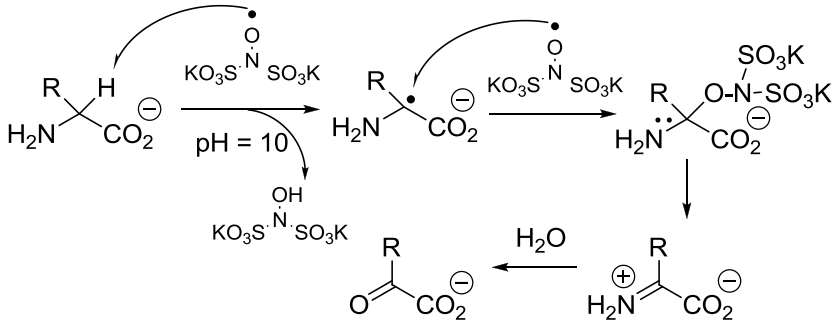
1.5.3 Electron-Poor Nitroxides

Fremy's salt, potassium nitrosodisulfonate, was the first reported nitroxide. The applications of Fremy's salt in synthesis have been reviewed by both Zimmer[223] and Parker,[224] and include the oxidation of heteroatom-substituted aromatic compounds, such as phenols,[225,226] naphthols, indoles,[227] carbazoles, quinolines,[228] benzylic alcohols,[229] and α-amino and α-hydroxy acids.[230,231] In the oxidation of phenols to benzoquinones,[232] very electron poor Fremy's nitroxide abstracts the phenolic hydrogen to give a resonance-stabilized phenoxy radical intermediate (**Scheme 1.24**). This delocalized radical is trapped at carbon with another Fremy's nitroxide, followed by elimination of the aminosulfonate group to provide the *ortho*- or *para*- benzoquinones. Amino acids can be oxidized by Fremy's



Scheme 1.24 Mechanism for the oxidation of phenol to benzoquinone with Fremy's salt

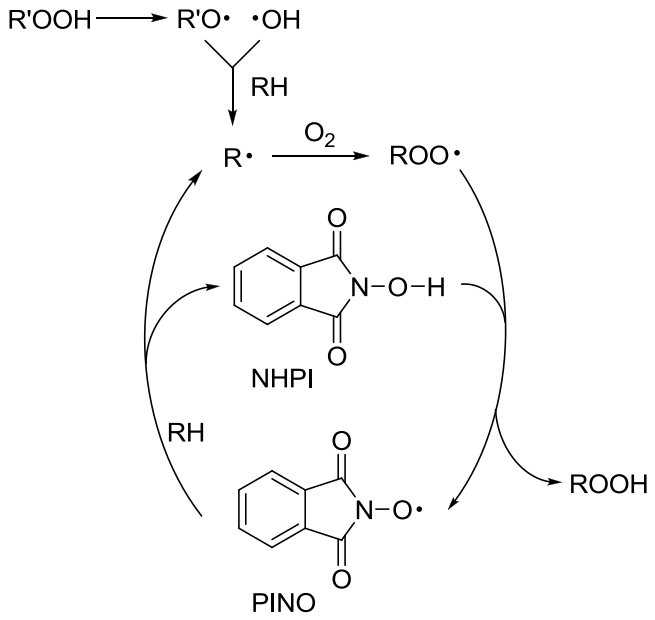
salt, followed by hydrolysis to the corresponding α-keto acids (**Scheme 1.25**).[231]



Scheme 1.25 Mechanism for the oxidation of amino acids to α-keto acids with Fremy's salt

Oxidation of phenols or anilines to quinines by Fremy's salt has been used in the total synthesis of several biologically active compounds.[233-236]

In contrast to stable dialkyl nitroxides, the diacyl nitroxide PINO, generated from *N*-hydroxyphthalimide (NHPI) (**Scheme 1.26**), is far more reactive at hydrogen atom abstraction than TEMPO due to the higher bond dissociation energy (BDE) of NO-H bond in PINO-H.[237] The electron withdrawing carbonyl groups destabilize the diacyl nitroxide, but increase the stability of the hydroxylamine via intramolecular



Scheme 1.26 Mechanism of autooxidation catalyzed by NHPI/peroxide

hydrogen bonding.[196] The reactivity of PINO can be tuned by adding substituents to the aromatic moiety.[238] PINO in combination with *m*-chloroperbenzoic acid,

$(NH_4)_5H_6PV_8Mo_4O_{40}$, or $Co(OAc)_2$ and O_2 (the Ishii System) as an initiator has been used to oxidize alcohols to aldehydes or ketones,[5,239-243] to oxidatively cleave benzylidene acetals[244] and to effect the autooxidation of unactivated alkanes and alkyl aromatics.[240,245-247] For example, aerobic oxidations to prepare commercially important fine chemicals, such as benzoic acid[248] and nicotinic acid (vitamin B_3)[249] can be performed in acetic acid under relatively mild conditions. A suggested mechanism in the presence of peroxide as an initiator is shown in **Scheme 1.26**.[250] Initiation involves formation of a radical species, followed by abstraction of hydrogen atom from NHPI to form PINO, which then propagates the radical chain.

The nitroxide generated from *N*, *N*′, *N*′′-trihydroxyisocyanuric acid (THICA) (**Figure 1.4**) can be more effective than PINO in hydrogen abstraction, probably due to the greater stability of the corresponding nitroxide against decomposition.[251] *N*-Hydroxysaccharin (NHS) (**Figure 1.4**), in which one carbonyl group of NHPI has been replaced by the more strongly electron withdrawing sulfonyl group, was shown to be

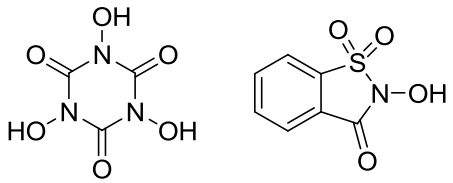


Figure 1.4 Precursors to highly reactive (nonpersistent) nitroxides utilized in autooxidation

a highly effective catalyst in the autooxidation of large-ring cycloalkanes,[252,253] under conditions where PINO did not work. NHS also catalyzes oxidation at benzylic positions, in addition to primary and secondary alcohols,[239,253] however the rates are lower than with NHPI.[239]

In contrast to electron-poor nitroxides, hydrogen atom abstraction by TEMPO under normal reaction conditions is not efficient due to the weak O-H bond in TEMPOH. However upon photoexcitation, TEMPO is much more reactive, and is able to abstract hydrogen atoms from solvents such as toluene, xylene[254,255] and acetonitrile[256] as well as cyclohexene,[257-259] phenols,[260,261] and even unactivated hydrocarbons.[262] However, the use of photoexcited nitroxides in hydrogen abstraction reactions has not yet been developed into synthetically viable procedures.

1.6 Conclusion

The use of nitroxides in synthetic organic chemistry has blossomed over the last 15 years. While nitroxides were largely used as spin labels in the past, nitroxides are now common reagents in synthesis, operating as oxidizing agents, and carbon radical traps. The oxoammonium salts act as both electrophiles and single electron oxidants, whereas the hydroxyamine anions act as both nucleophiles and single electron reductants. In redox processes, the nitroxide can often be used in catalytic

amounts, allowing the use of inexpensive primary oxidants. Applications to the oxidation of organic molecules, metal catalysts, and metal complexes are growing at an accelerating rate. Electron-poor nitroxides take part in a different manifold of reactions, abstracting hydrogen atoms in a variety of processes (including autooxidation), and adding to unsaturation. A number of highly designed nitroxides are emerging with specific properties, ranging from bridged, sterically unhindered nitroxides, nitroxides bearing an α-hydrogen (providing a slow but important decomposition pathway), electron-poor nitroxides, and nitroxides with appended functionality, including fluorophores, solubility tags, and reactive groups to allow for further synthetic elaboration. The commercial availability of TEMPO makes it the most popular of the nitroxide reagents; however as the chemistry becomes highly developed, it is inevitable that a variety of nitroxides will become regular reagents in the synthetic organic laboratory.

1.7 References

1. Bobbitt, J. M.; Flores, M. C. L., *Heterocycles* **1988,** *27* (2), 509-533.

2. Yamaguchi, M.; Miyazawa, T.; Takata, T.; Endo, T., *Pure and Applied Chemistry* **1990,** *62* (2), 217-222.

3. deNooy, A. E. J.; Besemer, A. C.; vanBekkum, H., *Synthesis-Stuttgart* **1996,** (10), 1153-1174.

4. Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A., *Chemical Reviews* **2001,** *101* (11), 3499-3548.

5. Sheldon, R. A.; Arends, I.; Ten Brink, G. J.; Dijksman, A., *Accounts of Chemical Research* **2002,** *35* (9), 774-781.

6. Merbouh, N.; Bobbitt, J. M.; Bruckner, C., *Organic Preparations and Procedures International* **2004,** *36* (1), 1-31.

7. Iwabuchi, Y., *Journal of Synthetic Organic Chemistry Japan* **2008,** *66* (11), 1076-1084.

8. Schoning, K. U., *Chimica Oggi-Chemistry Today* **2010,** *28* (1), 18-23.

9. Ciriminna, R.; Pagliaro, M., *Organic Process Research & Development* **2010,** *14* (1), 245-251.

10. Ponedel'kina, I. Y.; Khaibrakhmanova, E. A.; Odinokov, V. N., *Russian Chemical Reviews* **2010,** *79* (1), 63-75.

11. Tebben, L.; Studer, A., *Angewandte Chemie-International Edition* **2011,** *50* (22), 5034-5068.

12. Minisci, F.; Recupero, F.; Pedulli, G. F.; Lucarini, M., *Journal of Molecular Catalysis A-Chemical* **2003,** *204*, 63-90.

13. Golubev, V. A.; Borislavskii, V. N.; Aleksandrov, A. L., *Bulletin of the Academy of Sciences of the Ussr Division of Chemical Science* **1977,** *26* (9), 1874-1881.

14. Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M., *Journal of Organic Chemistry* **1985,** *50* (8), 1332-1334.

15. Merbouh, N.; Bobbitt, J. M.; Bruckner, C., *Journal of Organic Chemistry* **2004,** *69* (15), 5116-5119.

16. Bobbitt, J. M., *Journal of Organic Chemistry* **1998,** *63* (25), 9367-9374.

17. Bobbitt, J. M., *Molecules* **1999,** *4* (9), M102.

18. Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B., *Journal of Organic Chemistry* **2007,** *72* (12), 4504-4509.

19. Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F., *Journal of Organic Chemistry* **2009,** *74* (24), 9524-9527.

20. Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A., *Tetrahedron Letters* **1986,** *27* (10), 1119-1122.

21. Zakrzewski, J.; Grodner, J.; Bobbitt, J. M.; Karpinska, M., *Synthesis-Stuttgart* **2007**, 2491-2494.

22. Weik, S.; Nicholson, G.; Jung, G.; Rademann, J., *Angewandte Chemie-International Edition* **2001,** *40* (8), 1436-1439.

23. Merbouh, N.; Bobbitt, J. M.; Bruckner, C., *Tetrahedron Letters* **2001,** *42* (50), 8793-8796.

24. Breton, T.; Bashiardes, G.; Leger, J. M.; Kokoh, K. B., *European Journal of Organic Chemistry* **2007,** (10), 1567-1570.

25. Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y., *Chemical Communications* **2009,** (13), 1739-1741.

26. Zhao, M. Z.; Li, J.; Mano, E.; Song, Z. G.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J., *Journal of Organic Chemistry* **1999,** *64* (7), 2564-2566.

27. Shibuya, M.; Tomizawa, M.; Iwabuchi, Y., *Journal of Organic Chemistry* **2008,** *73* (12), 4750-4752.

28. Ganem, B., *Journal of Organic Chemistry* **1975,** *40* (13), 1998-2000.

29. Rychnovsky, S. D.; Vaidyanathan, R., *Journal of Organic Chemistry* **1999,** *64* (1), 310-312.

30. Cella, J. A.; Kelley, J. A.; Kenehan, E. F., *Journal of Organic Chemistry* **1975,** *40* (12), 1860-1862.

31. Ma, Z.; Bobbitt, J. M., *Journal of Organic Chemistry* **1991,** *56* (21), 6110-6114.

32. Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M., *Journal of Organic Chemistry* **1994,** *59* (21), 6338-6343.

33. Bragd, P. L.; van Bekkum, H.; Besemer, A. C., *Topics in Catalysis* **2004,** *27* (1-4), 49-66.

34. Ben-Daniel, R.; Alsters, P.; Neumann, R., *Journal of Organic Chemistry* **2001,** *66* (25), 8650-8653.

35. Kim, S. S.; Jung, H. C., *Synthesis-Stuttgart* **2003,** (14), 2135-2137.

36. Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F., *Tetrahedron Letters* **2001,** *42* (38), 6651-6653.

37. Minisci, F.; Recupero, F.; Rodino, M.; Sala, M.; Schneider, A., *Organic Process Research & Development* **2003,** *7* (6), 794-798.

38. Bourbonnais, R.; Paice, M. G., *Febs Letters* **1990,** *267* (1), 99-102.

39. Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D., *Tetrahedron Letters* **2001,** *42* (43), 7551-7553.

40. Fabbrini, M.; Galli, C.; Gentili, P., *Journal of Molecular Catalysis B-Enzymatic* **2002,** *16* (5-6), 231-240.

41. Arends, I.; Li, Y. X.; Ausan, R.; Sheldon, R. A., *Tetrahedron* **2006,** *62* (28), 6659-6665.

42. d'Acunzo, F.; Baiocco, P.; Fabbrini, M.; Galli, C.; Gentili, P., *European Journal of Organic Chemistry* **2002,** (24), 4195-4201.

43. Arends, I.; Li, Y. X.; Sheldon, R. A., *Biocatalysis and Biotransformation* **2006,** *24* (6), 443-448.

44. Tromp, S. A.; Matijosyte, I.; Sheldon, R. A.; Arends, I.; Mul, G.; Kreutzer, M. T.; Moulijn, J. A.; de Vries, S., *Chemcatchem* **2010,** *2* (7), 827-833.

45. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S., *Journal of Organic Chemistry* **1987,** *52* (12), 2559-2562.

46. Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S., *Journal of Organic Chemistry* **1989,** *54* (12), 2970-2972.

47. Song, Z. G. J.; Zhao, M. Z.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E., *Journal of Organic Chemistry* **1999,** *64* (26), 9658-9667.

48. Zanka, A., *Chemical & Pharmaceutical Bulletin* **2003,** *51* (7), 888-889.

49. Davis, N. J.; Flitsch, S. L., *Tetrahedron Letters* **1993,** *34* (7), 1181-1184.

50. Milkereit, G.; Morr, M.; Thiem, J.; Vill, V., *Chemistry and Physics of Lipids* **2004,** *127* (1), 47-63.

51. Adorjan, I.; Jaaskelainen, A. S.; Vuorinen, T., *Carbohydrate Research* **2006,** *341* (14), 2439-2443.

52. Lemoine, S.; Thomazeau, C.; Joannard, D.; Trombotto, S.; Descotes, G.; Bouchu, A.; Queneau, Y., *Carbohydrate Research* **2000,** *326* (3), 176-184.

53. Kraus, T.; Budesinsky, M.; Zavada, J., *Journal of Organic Chemistry* **2001,** *66* (13), 4595-4600.

54. Denooy, A. E. J.; Besemer, A. C.; Vanbekkum, H., *Recueil Des Travaux Chimiques Des Pays-Bas-Journal of the Royal Netherlands Chemical Society* **1994,** *113* (3), 165-166.

55. Rundlof, T.; Widmalm, G., *Analytical Biochemistry* **1996,** *243* (2), 228-233.

56. Gomez-Bujedo, S.; Fleury, E.; Vignon, M. R., *Biomacromolecules* **2004,** *5* (2), 565-571.

57. Montanari, S.; Rountani, M.; Heux, L.; Vignon, M. R., *Macromolecules* **2005,** *38* (5), 1665-1671.

58. Habibi, Y.; Vignon, M. R., *Cellulose* **2008,** *15* (1), 177-185.

59. Leanna, M. R.; Sowin, T. J.; Morton, H. E., *Tetrahedron Letters* **1992,** *33* (35), 5029-5032.

60. Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P., *Tetrahedron* **1998,** *54* (22), 6051-6064.

61. Hampton, P. D.; Whealon, M. D.; Roberts, L. M.; Yaeger, A. A.; Boydson, R., *Organic Process Research & Development* **2008,** *12* (5), 946-949.

62. DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G., *Journal of Organic Chemistry* **1997,** *62* (20), 6974-6977.

63. Miller, R. A.; Hoerrner, R. S., *Organic Letters* **2003,** *5* (3), 285-287.

64. Kim, S. S.; Nehru, K., *Synlett* **2002,** (4), 616-618.

65. Liu, Z. Q.; Shang, X. J.; Chai, L. Z.; Sheng, Q. J., *Catalysis Letters* **2008,** *123* (3-4), 317-320.

66. Lei, M.; Hu, R. J.; Wang, Y. G., *Tetrahedron* **2006,** *62* (38), 8928-8932.

67. Zhao, X. F.; Zhang, C., *Synthesis-Stuttgart* **2007,** (4), 551-557.

68. Li, X. Q.; Zhang, C., *Synthesis-Stuttgart* **2009,** (7), 1163-1169.

69. Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L., *Journal of Organic Chemistry* **1996,** *61* (21), 7452-7454.

70. Bolm, C.; Magnus, A. S.; Hildebrand, J. P., *Organic Letters* **2000,** *2* (8), 1173-1175.

71. Jiang, N.; Ragauskas, A. J., *Tetrahedron Letters* **2005,** *46* (19), 3323-3326.

72. Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S., *Journal of Organic Chemistry* **1990,** *55* (2), 462-466.

73. Mei, Z. W.; Omote, T.; Mansour, M.; Kawafuchi, H.; Takaguchi, Y.; Jutand, A.; Tsuboi, S.; Inokuchi, T., *Tetrahedron* **2008,** *64* (47), 10761-10766.

74. Mei, Z. W.; Ma, L. J.; Kawafuchi, H.; Okihara, T.; Inokuchi, T., *Bulletin of the Chemical Society of Japan* **2009,** *82* (8), 1000-1002.

75. De Luca, L.; Giacomelli, G.; Porcheddu, A., *Organic Letters* **2001,** *3* (19), 3041-3043.

76. De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A., *Journal of Organic Chemistry* **2003,** *68* (12), 4999-5001.

77. Yadav, J. S.; Rajender, V.; Rao, Y. G., *Organic Letters* **2010,** *12* (2), 348-350.

78. Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S.; Danishefsky, S. J., *Journal of Organic Chemistry* **2005,** *70* (26), 10619-10637.

79. Sarabia, F.; Sanchez-Ruiz, A., *Journal of Organic Chemistry* **2005,** *70* (23), 9514-9520.

80. Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J. H.; Abrams, J. N.; Forsyth, C. J., *Tetrahedron Letters* **2003,** *44* (1), 57-59.

81. Herrerias, C. I.; Zhang, T. Y.; Li, C. J., *Tetrahedron Letters* **2006,** *47* (1), 13-17.

82. Shibuya, M.; Tomizawa, M.; Iwabuchi, Y., *Organic Letters* **2008,** *10* (21), 4715-4718.

83. Vatele, J. M., *Synlett* **2008,** (12), 1785-1788.

84. Vatele, J. M., *Tetrahedron* **2010,** *66* (4), 904-912.

85. Rychnovsky, S. D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P. J., *Journal of Organic Chemistry* **1999,** *64* (18), 6745-6749.

86. Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y., *Journal of the American Chemical Society* **2006,** *128* (26), 8412-8413.

87. Shibuya, M.; Sasano, Y.; Tomizawa, M.; Hamada, T.; Kozawa, M.; Nagahama, N.; Iwabuchi, Y., *Synthesis-Stuttgart* **2011,** (21), 3418-3425.

88. Shibuya, M.; Osada, Y.; Sasano, Y.; Tomizawa, M.; Iwabuchi, Y., *Journal of the American Chemical Society* **2011,** *133* (17), 6497-6500.

89. Hayashi, M.; Sasano, Y.; Nagasawa, S.; Shibuya, M.; Iwabuchi, Y., *Chemical & Pharmaceutical Bulletin* **2011,** *59* (12), 1570-1573.

90. Demizu, Y.; Shiigi, H.; Oda, T.; Matsumura, Y.; Onomura, O., *Tetrahedron Letters* **2008,** *49* (1), 48-52.

91. Shibuya, M.; Tomizawa, M.; Sasano, Y.; Iwabuchi, Y., *Journal of Organic Chemistry* **2009,** *74* (12), 4619-4622.

92. Liu, R. H.; Liang, X. M.; Dong, C. Y.; Hu, X. Q., *Journal of the American Chemical Society* **2004,** *126* (13), 4112-4113.

93. Wang, X. L.; Liu, R. H.; Jin, Y.; Liang, X. M., *Chemistry-A European Journal* **2008,** *14* (9), 2679-2685.

94. Liu, R. H.; Dong, C. Y.; Liang, X. M.; Wang, X. J.; Hu, X. Q., *Journal of Organic Chemistry* **2005,** *70* (2), 729-731.

95. Xie, Y.; Mo, W. M.; Xu, D.; Shen, Z. L.; Sun, N.; Hu, B. X.; Hu, X. Q., *Journal of Organic Chemistry* **2007,** *72* (11), 4288-4291.

96. He, X. J.; Shen, Z. L.; Mo, W. M.; Sun, N.; Hu, B. X.; Hu, X. Q., *Advanced Synthesis & Catalysis* **2009,** *351* (1-2), 89-92.

97. Wertz, S.; Studer, A., *Advanced Synthesis & Catalysis* **2011,** *353* (1), 69-72.

98. Yang, G. Y.; Wang, W.; Zhu, W. M.; An, C. B.; Gao, X. Q.; Song, M. P., *Synlett* **2010,** (3), 437-440.

99. Bolm, C.; Fey, T., *Chemical Communications* **1999,** (18), 1795-1796.

100. Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C., *Journal of Organic Chemistry* **2001,** *66* (24), 8154-8159.

101. Karimi, B.; Biglari, A.; Clark, J. H.; Budarin, V., *Angewandte Chemie-International Edition* **2007,** *46*, 7210-7213.

102. Brunel, D.; Fajula, F.; Nagy, J. B.; Deroide, B.; Verhoef, M. J.; Veum, L.; Peters, J. A.; van Bekkum, H., *Applied Catalysis A-General* **2001,** *213* (1), 73-82.

103. Ciriminna, R.; Blum, J.; Avnir, D.; Pagliaro, M., *Chemical Communications* **2000,** (15), 1441-1442.

104. Ciriminna, R.; Bolm, C.; Fey, T.; Pagliaro, M., *Advanced Synthesis & Catalysis* **2002,** *344* (2), 159-163.

105. Testa, M. L.; Ciriminna, R.; Hajji, C.; Garcia, E. Z.; Ciclosi, M.; Arques, J. S.; Pagliaro, M., *Advanced Synthesis & Catalysis* **2004,** *346* (6), 655-660.

106. Gilhespy, M.; Lok, M.; Baucherel, X., *Chemical Communications* **2005,** (8), 1085-1086.

107. Ferreira, P.; Hayes, W.; Phillips, E.; Rippon, D.; Tsang, S. C., *Green Chemistry* **2004,** *6* (7), 310-312.

108. Michaud, A.; Gingras, G.; Morin, M.; Beland, F.; Ciriminna, R.; Avnir, D.; Pagliaro, M., *Organic Process Research & Development* **2007,** *11* (4), 766-768.

109. Gilhespy, M.; Lok, M.; Baucherel, X., *Catalysis Today* **2006,** *117* (1-3), 114-119.

110. Dijksman, A.; Arends, I.; Sheldon, R. A., *Synlett* **2001,** (1), 102-104.

111. Tanyeli, C.; Gumus, A., *Tetrahedron Letters* **2003,** *44* (8), 1639-1642.

112. Subhani, M. A.; Beigi, M.; Eilbracht, P., *Advanced Synthesis & Catalysis* **2008,** *350* (18), 2903-2909.

113. Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C., *Applied Catalysis B-Environmental* **2005,** *61* (3-4), 206-211.

114. Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C.; Hayes, W., *Journal of Organic Chemistry* **2004,** *69* (20), 6851-6859.

115. Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G., *Organic Letters* **2004,** *6* (3), 441-443.

116. Luo, J. T.; Pardin, C.; Lubell, W. D.; Zhu, X. X., *Chemical Communications* **2007,** (21), 2136-2138.

117. Benaglia, M.; Puglisi, A.; Holczknecht, O.; Quici, S.; Pozzi, G., *Tetrahedron* **2005,** *61* (51), 12058-12064.

118. Miao, C. X.; He, L. N.; Wang, J. Q.; Gao, J., *Synlett* **2009,** (20), 3291-3294.

119. Dijksman, A. E.; Arends, I.; Sheldon, R. A., *Chemical Communications* **2000,** (4), 271-272.

120. Gheorghe, A.; Matsuno, A.; Reiser, O., *Advanced Synthesis & Catalysis* **2006,** *348* (9), 1016-1020.

121. Kashiwagi, Y.; Ikezoe, H.; Ono, T., *Synlett* **2006,** (1), 69-72.

122. Mason, B. P.; Bogdan, A. R.; Goswami, A.; McQuade, D. T., *Organic Letters* **2007,** *9*, 3449-3451.

123. Lindner, J. P.; Roben, C.; Studer, A.; Stasiak, M.; Ronge, R.; Greiner, A.; Wendorff, H. J., *Angewandte Chemie-International Edition* **2009,** *48* (47), 8874-8877.

124. Kubota, J.; Ido, T.; Kuroboshi, M.; Tanaka, H.; Uchida, T.; Shimamura, K., *Tetrahedron* **2006,** *62* (20), 4769-4773.

125. Sakuratani, K.; Togo, H., *Synthesis-Stuttgart* **2003,** (1), 21-23.

126. Tashino, Y.; Togo, H., *Synlett* **2004,** (11), 2010-2012.

127. But, T. Y. S.; Tashino, Y.; Togo, H.; Toy, P. H., *Organic & Biomolecular Chemistry* **2005,** *3* (6), 970-971.

128. Sourkouni-Argirusi, G.; Kirschning, A., *Organic Letters* **2000,** *2* (24), 3781-3784.

129. Brunjes, M.; Sourkouni-Argirusi, G.; Kirschning, A., *Advanced Synthesis & Catalysis* **2003,** *345* (5), 635-642.

130. Yasuda, K.; Ley, S. V., *Journal of the Chemical Society-Perkin Transactions 1* **2002,** (8), 1024-1025.

131. Kloth, K.; Brunjes, M.; Kunst, E.; Joge, T.; Gallier, F.; Adibekian, A.; Kirschning, A., *Advanced Synthesis & Catalysis* **2005,** *347* (10), 1423-1434.

132. Qian, W. X.; Jin, E. L.; Bo, W. L.; Zhang, Y. M., *Tetrahedron* **2006,** *62* (4), 556-562.

133. Wu, X. E.; Ma, L.; Ding, M. X.; Gao, L. X., *Synlett* **2005,** (4), 607-610.

134. Miao, C. X.; He, L. N.; Wang, J. Q.; Wang, J. L., *Advanced Synthesis & Catalysis* **2009,** *351* (13), 2209-2216.

135. Wu, X. E.; Ma, L.; Ding, M. X.; Gao, L. X., *Chemistry Letters* **2005,** *34* (3), 312-313.

136. Jiang, N.; Ragauskas, A. J., *Organic Letters* **2005,** *7* (17), 3689-3692.

137. Holczknecht, O.; Cavazzini, M.; Quici, S.; Shepperson, I.; Pozzi, G., *Advanced Synthesis & Catalysis* **2005,** *347* (5), 677-688.

138. Gheorghe, A.; Cuevas-Yanez, E.; Horn, J.; Bannwarth, W.; Narsaiah, B.; Reiser, O., *Synlett* **2006**, 2767-2770.

139. Gheorghe, A.; Chinnusamy, T.; Cuevas-Yanez, E.; Hilgers, P.; Reiser, O., *Organic Letters* **2008,** *10* (19), 4171-4174.

140. Dobbs, A. P.; Jones, P.; Penny, M. J.; Rigby, S. E., *Tetrahedron* **2009,** *65* (27), 5271-5277.

141. Holczknecht, O.; Pozzi, G.; Quici, S., *Qsar & Combinatorial Science* **2006,** *25* (8-9), 736-741.

142. Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P., *Tetrahedron Letters* **2000,** *41* (22), 4343-4346.

143. Ragagnin, G.; Betzemeier, B.; Quici, S.; Knochel, P., *Tetrahedron* **2002,** *58* (20), 3985-3991.

144. Lu, N.; Lin, Y. C., *Tetrahedron Letters* **2007,** *48* (50), 8823-8828.

145. Roben, C.; Studer, A.; Hemme, W. L.; Eckert, H., *Synlett* **2010,** (7), 1110-1114.

146. Schatz, A.; Grass, R. N.; Stark, W. J.; Reiser, O., *Chemistry-A European Journal* **2008,** *14* (27), 8262-8266.

147. Manda, S.; Nakanishi, I.; Ohkubo, K.; Kawashima, T.; Matsumoto, K.; Ozawa, T.; Fukuzumi, S.; Ikota, N.; Anzai, K., *Chemistry Letters* **2007,** *36* (7), 914-915.

148. Semmelhack, M. F.; Chou, C. S.; Cortes, D. A., *Journal of the American Chemical Society* **1983,** *105* (13), 4492-4494.

149. Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T., *Heterocycles* **1999,** *51* (8), 1945-1948.

150. Schamann, M.; Schafer, H. J., *European Journal of Organic Chemistry* **2003,** (2), 351-358.

151. Kubota, J.; Shimizu, Y.; Mitsudo, K.; Tanaka, H., *Tetrahedron Letters* **2005,** *46* (52), 8975-8979.

152. Mitsudo, K.; Kumagai, H.; Takabatake, F.; Kubota, J.; Tanaka, H., *Tetrahedron Letters* **2007,** *48* (51), 8994-8997.

153. Kuroboshi, M.; Goto, K.; Tanaka, H., *Synthesis-Stuttgart* **2009,** (6), 903-908.

154. Palmisano, G.; Ciriminna, R.; Pagliaro, M., *Advanced Synthesis & Catalysis* **2006,** *348* (15), 2033-2037.

155. Osa, T.; Kashiwagi, Y.; Mukai, K.; Ohsawa, A.; Bobbitt, J. M., *Chemistry Letters* **1990,** (1), 75-78.

156. Merz, A.; Bachmann, H., *Journal of the American Chemical Society* **1995,** *117* (3), 901-908.

157. Geneste, F.; Moinet, C.; Ababou-Girard, S.; Solal, F., *New Journal of Chemistry* **2005,** *29* (12), 1520-1526.

158. Kashiwagi, Y.; Nishimura, T.; Anzai, J., *Electrochimica Acta* **2002,** *47* (8), 1317-1320.

159. Barhdadi, R.; Comminges, C.; Doherty, A. P.; Nedelec, J. Y.; O'Toole, S.; Troupel, M., *Journal of Applied Electrochemistry* **2007,** *37* (6), 723-728.

160. Schamann, A.; Schafer, H. J., *Electrochimica Acta* **2005,** *50* (25-26), 4956-4972.

161. Schnatbaum, K.; Schafer, H. J., *Synthesis-Stuttgart* **1999,** (5), 864-872.

162. Zhang, M. A.; Chen, C. C.; Ma, W. H.; Zhao, J. C., *Angewandte Chemie-International Edition* **2008,** *47* (50), 9730-9733.

163. Nagasawa, T.; Allakhverdiev, S. I.; Kimura, Y.; Nagata, T., *Photochemical & Photobiological Sciences* **2009,** *8* (2), 174-180.

164. Naik, N.; Braslau, R., *Tetrahedron* **1998,** *54* (5-6), 667-696.

165. Ma, Z. K.; Huang, Q. T.; Bobbitt, J. M., *Journal of Organic Chemistry* **1993,** *58* (18), 4837-4843.

166. Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Tetrahedron Letters* **1999,** *40* (35), 6469-6472.

167. Kashiwagi, Y.; Kurashima, F.; Chiba, S.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemical Communications* **2003,** (1), 114-115.

168. Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H., *Journal of Organic Chemistry* **1996,** *61* (4), 1194-1195.

169. Formaggio, F.; Bonchio, M.; Crisma, M.; Peggion, C.; Mezzato, S.; Polese, A.; Barazza, A.; Antonello, S.; Maran, F.; Broxterman, Q. B.; Kaptein, B.; Kamphuis, J.; Vitale, R. M.; Saviano, M.; Benedetti, E.; Toniolo, C., *Chemistry-A European Journal* **2002,** *8* (1), 84-93.

170. Kuroboshi, M.; Yoshihisa, H.; Cortona, M. N.; Kawakami, Y.; Gao, Z.; Tanaka, H., *Tetrahedron Letters* **2000,** *41* (42), 8131-8135.

171. Graetz, B.; Rychnovsky, S.; Leu, W. H.; Farmer, P.; Lin, R., *Tetrahedron-Asymmetry* **2005,** *16* (21), 3584-3598.

172. Tomizawa, M.; Shibuya, M.; Iwabuchi, Y., *Organic Letters* **2009,** *11* (8), 1829-1831.

173. Yamakoshi, H.; Shibuya, M.; Tomizawa, M.; Osada, Y.; Kanoh, N.; Iwabuchi, Y., *Organic Letters* **2010,** *12* (5), 980-983.

174. Kashiwagi, Y.; Yanagisawa, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemical Communications* **1996,** (24), 2745-2746.

175. Yanagisawa, Y.; Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemistry Letters* **1996,** (12), 1043-1044.

176. Mannam, S.; Sekar, G., *Tetrahedron-Asymmetry* **2009,** *20* (4), 497-502.

177. Alamsetti, S. K.; Mannam, S.; Mutupandi, P.; Sekar, G., *Chemistry-A European Journal* **2009,** *15* (5), 1086-1090.

178. Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemical Communications* **1999,** (19), 1983-1984.

179. Nechab, M.; Kumar, D. N.; Philouze, C.; Einhorn, C.; Einhorn, J., *Angewandte Chemie-International Edition* **2007,** *46* (17), 3080-3083.

180. Perkins, M. J.; Berti, C.; Brooks, D. J.; Grierson, L.; Grimes, J. A. M.; Jenkins, T. C.; Smith, S. L., *Pure and Applied Chemistry* **1990,** *62* (2), 195-200.

181. Einhorn, C.; Einhorn, J.; Marcadal-Abbadi, C.; Pierre, J. L., *Journal of Organic Chemistry* **1999,** *64* (12), 4542-4546.

182. Siedlecka, R.; Skarzewski, J.; Mlochowski, J., *Tetrahedron Letters* **1990,** *31* (15), 2177-2180.

183. Siedlecka, R.; Skarzewski, J., *Synthesis-Stuttgart* **1994,** (4), 401-404.

184. Siedlecka, R.; Skarzewski, J., *Synlett* **1996,** (8), 757-758.

185. Huang, J. Y.; Li, S. J.; Wang, Y. G., *Tetrahedron Letters* **2006,** *47* (32), 5637-5640.

186. Velusamy, S.; Kumar, A. V.; Saini, R.; Punniyamurthy, T., *Tetrahedron Letters* **2005,** *46* (22), 3819-3822.

187. Kashiwagi, Y.; Ohsawa, A.; Osa, T.; Ma, Z.; Bobbitt, J. M., *Chemistry Letters* **1991,** (4), 581-584.

188. Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F., *Organic Letters* **2006,** *8*, 5485-5487.

189. Breton, T.; Liaigre, D.; Belgsir, E., *Tetrahedron Letters* **2005,** *46* (14), 2487-2490.

190. Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z. K.; Tang, H. T., *Heterocycles* **1990,** *30* (2), 1131-1140.

191. Miyazawa, T.; Endo, T., *Tetrahedron Letters* **1986,** *27* (29), 3395-3398.

192. Cho, N. S.; Park, C. H., *Bulletin of the Korean Chemical Society* **1994,** *15* (11), 924-926.

193. Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Urchegui, R.; Linden, A., *Journal of Organic Chemistry* **1996,** *61* (13), 4400-4404.

194. Palomo, C.; Oiarbide, M.; Esnal, A.; Landa, A.; Miranda, J. I.; Linden, A., *Journal of Organic Chemistry* **1998,** *63* (17), 5838-5846.

195. Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A.; Linden, A., *Journal of Organic Chemistry* **2001,** *66* (12), 4180-4186.

196. Sheldon, R. A.; Arends, I., *Journal of Molecular Catalysis A-Chemical* **2006,** *251* (1-2), 200-214.

197. Sheldon, R. A.; Arends, I., *Advanced Synthesis & Catalysis* **2004,** *346* (9-10), 1051-1071.

198. Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S., *Journal of the American Chemical Society* **1984,** *106* (11), 3374-3376.

199. Dijksman, A.; Arends, I.; Sheldon, R. A., *Organic & Biomolecular Chemistry* **2003,** *1* (18), 3232-3237.

200. Dijksman, A.; Marino-Gonzalez, A.; Payeras, A. M. I.; Arends, I.; Sheldon, R. A., *Journal of the American Chemical Society* **2001,** *123* (28), 6826-6833.

201. Whittaker, M. M.; Whittaker, J. W., *Biochemistry* **2001,** *40* (24), 7140-7148.

202. Wang, Y. D.; DuBois, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P., *Science* **1998,** *279* (5350), 537-540.

203. Gamez, P.; Arends, I.; Reedijk, J.; Sheldon, R. A., *Chemical Communications* **2003,** (19), 2414-2415.

204. Gamez, P.; Arends, I.; Sheldon, R. A.; Reedijk, J., *Advanced Synthesis & Catalysis* **2004,** *346* (7), 805-811.

205. Michel, C.; Belanzoni, P.; Gamez, P.; Reedijk, J.; Baerends, E. J., *Inorganic Chemistry* **2009,** *48* (24), 11909-11920.

206. Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C., *Journal of the American Chemical Society* **2010,** *132* (29), 10012-10014.

207. Kumpulainen, E. T. T.; Koskinen, A. M. P., *Chemistry-A European Journal* **2009,** *15* (41), 10901-10911.

208. Figiel, P. J.; Leskela, M.; Repo, T., *Advanced Synthesis & Catalysis* **2007,** *349* (7), 1173-1179.

209. Uber, J. S.; Vogels, Y.; van den Helder, D.; Mutikainen, I.; Turpeinen, U.; Fu, W. T.; Roubeau, O.; Gamez, P.; Reedijk, J., *European Journal of Inorganic Chemistry* **2007**, 4197-4206.

210. Mannam, S.; Alamsetti, S. K.; Sekar, G., *Advanced Synthesis & Catalysis* **2007,** *349*, 2253-2258.

211. Velusamy, S.; Srinivasan, A.; Punniyamurthy, T., *Tetrahedron Letters* **2006,** *47* (6), 923-926.

212. Herbert, M.; Montilla, F.; Galindo, A., *Dalton Transactions* **2010,** *39* (3), 900-907.

213. Vatele, J. M., *Synlett* **2009,** (13), 2143-2145.

214. Dijksman, A.; Arends, I.; Sheldon, R. A., *Chemical Communications* **1999,** (16), 1591-1592.

215. Robinson, R. S.; Taylor, R. J. K., *Synlett* **2005,** (6), 1003-1005.

216. Wang, N. W.; Liu, R. H.; Chen, J. P.; Liang, X. M., *Chemical Communications* **2005**, 5322-5324.

217. Yin, W. L.; Chu, C. H.; Lu, Q. Q.; Tao, J. W.; Liang, X. M.; Liu, R. H., *Advanced Synthesis & Catalysis* **2010,** *352* (1), 113-118.

218. Kumar, R. S.; Karthikeyan, K.; Perumal, P. T., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2008,** *86* (7), 720-725.

219. Kaizer, J.; Pap, J.; Speier, G., *Food Chemistry* **2005,** *93* (3), 425-430.

220. Kaizer, J.; Csonka, R.; Speier, G., *Journal of Molecular Catalysis A-Chemical* **2002,** *180* (1-2), 91-96.

221. Wen, X. L.; Jia, Y. H.; Yang, L.; Liu, Z. L., *Talanta* **2001,** *53* (5), 1031-1036.

222. Kaizer, J.; Csonka, R.; Speier, G., *Reaction Kinetics and Catalysis Letters* **2002,** *75* (2), 367-374.

223. Zimmer, H.; Lankin, D. C.; Horgan, S. W., *Chemical Reviews* **1971,** *71* (2), 229-246.

224. Parker, K. A.; Su, D.-S., *Encyclopedia of Reagents for Organic Synthesis*. John Wiley: New York, 1995.

225. Kawle, B.; Adinarayana, M., *Indian Journal of Chemistry Section a-Inorganic Bio-Inorganic Physical Theoretical & Analytical Chemistry* **1994,** *33* (2), 124-127.

226. Leyva, E.; Crispin, I.; Moctezuma, E.; Leyva, S., *Arkivoc* **2003**, 203-212.

227. Giethlen, B.; Schaus, J. M., *Tetrahedron Letters* **1997,** *38* (49), 8483-8486.

228. Kitahara, Y.; Nakai, T.; Nakahara, S.; Akazawa, M.; Shimizu, M.; Kubo, A., *Chemical & Pharmaceutical Bulletin* **1991,** *39* (9), 2256-2263.

229. De, P.; Kumar, D. P.; Mondal, A. K.; Mandal, P. C.; Mukhopadhyay, S.; Banerjee, R., *Polyhedron* **2010,** *29* (4), 1358-1362.

230. Kawle, B.; Rao, M. T.; Adinarayana, M., *Indian Journal of Chemistry Section a-Inorganic Bio-Inorganic Physical Theoretical & Analytical Chemistry* **1994,** *33* (11), 1021-1023.

231. Kawle, B.; Rao, M. T.; Adinarayana, M., *Indian Journal of Chemistry Section a-Inorganic Bio-Inorganic Physical Theoretical & Analytical Chemistry* **1996,** *35* (8), 667-670.

232. Teuber, H. J.; Gross, H. J., *Chemische Berichte-Recueil* **1975,** *108* (6), 2097-2106.

233. Boger, D. L.; Cassidy, K. C.; Nakahara, S., *Journal of the American Chemical Society* **1993,** *115* (23), 10733-10741.

234. Kinugawa, M.; Masuda, Y.; Arai, H.; Nishikawa, H.; Ogasa, T.; Tomioka, S.; Kasai, M., *Synthesis-Stuttgart* **1996,** (5), 633-636.

235. Matsumoto, N.; Iinuma, H.; Sawa, T.; Takeuchi, T., *Bioorganic & Medicinal Chemistry Letters* **1998,** *8* (21), 2945-2948.

236. Kraus, G. A.; Selvakumar, N., *Journal of Organic Chemistry* **1998,** *63* (26), 9846-9849.

237. Annunziatini, C.; Gerini, M. F.; Lanzalunga, O.; Lucarini, M., *Journal of Organic Chemistry* **2004,** *69* (10), 3431-3438.

238. Baciocchi, E.; Calcagni, A.; Lanzalunga, O., *Journal of Organic Chemistry* **2008,** *73* (11), 4110-4115.

239. Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y., *Tetrahedron Letters* **1995,** *36* (38), 6923-6926.

240. Ishii, Y.; Sakaguchi, S., *Catalysis Surveys from Japan* **1999,** *3* (1), 27-35.

241. Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F., *Chemical Communications* **2002,** (7), 688-689.

242. d'Acunzo, F.; Baiocco, P.; Fabbrini, M.; Galli, C.; Gentili, P., *New Journal of Chemistry* **2002,** *26* (12), 1791-1794.

243. Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F., *European Journal of Organic Chemistry* **2004,** (1), 109-119.

244. Chen, Y. S.; Wang, P. G., *Tetrahedron Letters* **2001,** *42* (30), 4955-4958.

245. Fukuda, O.; Sakaguchi, S.; Ishii, Y., *Advanced Synthesis & Catalysis* **2001,** *343* (8), 809-813.

246. Sawatari, N.; Yokota, T.; Sakaguchi, S.; Ishii, Y., *Journal of Organic Chemistry* **2001,** *66* (23), 7889-7891.

247. Toribio, P. P.; Gimeno-Gargallo, A.; Capel-Sanchez, M. C.; de Frutos, M. P.; Campos-Martin, J. M.; Fierro, J. L. G., *Applied Catalysis A-General* **2009,** *363* (1-2), 32-39.

248. Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y., *Journal of Organic Chemistry* **1997,** *62* (20), 6810-6813.

249. Shibamoto, A.; Sakaguchi, S.; Ishii, Y., *Organic Process Research & Development* **2000,** *4* (6), 505-508.

250. Hermans, I.; Vereecken, L.; Jacobs, P. A.; Peeters, J., *Chemical Communications* **2004,** (9), 1140-1141.

251. Hirai, N.; Sawatari, N.; Nakamura, N.; Sakaguchi, S.; Ishii, Y., *Journal of Organic Chemistry* **2003,** *68* (17), 6587-6590.

252. Baucherel, X.; Arends, I.; Ellwood, S.; Sheldon, R. A., *Organic Process Research & Development* **2003,** *7* (3), 426-428.

253. Baucherel, X.; Gonsalvi, L.; Arends, I.; Ellwood, S.; Sheldon, R. A., *Advanced Synthesis & Catalysis* **2004,** *346* (2-3), 286-296.

254. Keana, J. F. W.; Dinerste.Rj; Baitis, F., *Journal of Organic Chemistry* **1971,** *36* (1), 209-211.

255. Opeida, I. A.; Matvienko, A. G.; Ostrovskaya, O. Z., *Kinetics and Catalysis* **1995,** *36* (3), 441-441.

256. Johnston, L. J.; Tencer, M.; Scaiano, J. C., *Journal of Organic Chemistry* **1986,** *51* (14), 2806-2808.

257. Bottle, S. E.; Busfield, W. K.; Jenkins, I. D., *Journal of the Chemical Society-Perkin Transactions 2* **1992,** (12), 2145-2150.

258. Babiarz, J. E.; Cunkle, G. T.; DeBellis, A. D.; Eveland, D.; Pastor, S. D.; Shum, S. P., *Journal of Organic Chemistry* **2002,** *67* (19), 6831-6834.

259. Coseri, S.; Ingold, K. U., *Organic Letters* **2004,** *6* (10), 1641-1643.

260. Aliaga, C.; Juarez-Ruiz, J. M.; Scaiano, J. C.; Aspee, A., *Organic Letters* **2008,** *10* (11), 2147-2150.

261. Aliaga, C.; Rezende, M. C.; Tirapegui, C., *Tetrahedron* **2009,** *65* (31), 6025-6028.

262. Bottle, S. E.; Chand, U.; Micallef, A. S., *Chemistry Letters* **1997,** (9), 857-858.

Chapter 2: Introduction to Profluorescent Nitroxides and Nitroxide-Quantum Dot Sensors

2.1 Nitroxides

Nitroxides are kinetically persistent *N*,*N*-disubstituted NO free radicals. Many are stable, commercially available compounds, and can be handled in the laboratory without any special requirements. The stability is attributed to two factors: resonance stabilization due to an unpaired electron delocalized between the nitrogen and the oxygen atom as shown in **Figure 2.1**, and steric hindrance from bulky substituents attached to the nitrogen atom.[1] The spin density is distributed between both atoms, often with a slightly higher density at the oxygen atom.[2]

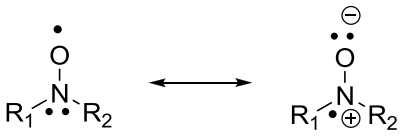


Figure 2.1 Resonance stabilization of a nitroxide

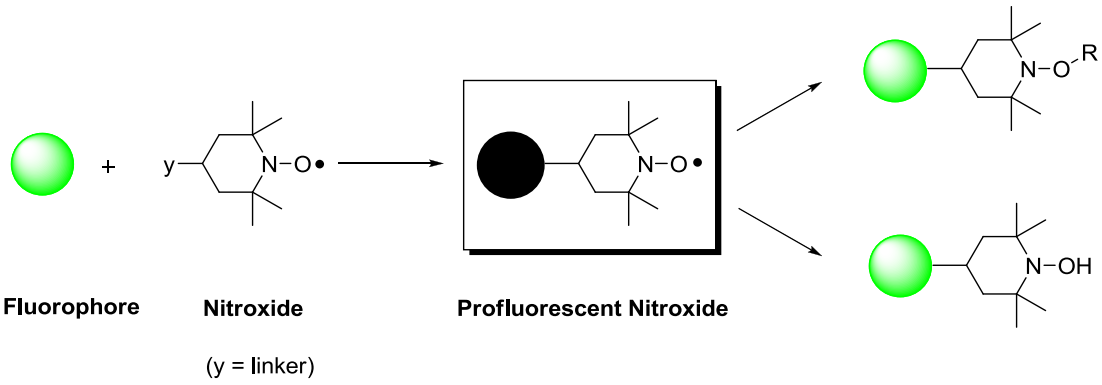
Because of their paramagnetic properties, nitroxides have been utilized in a wide variety of fields, such as 'spin labels' or 'spin probes' in electron paramagnetic resonance (EPR) for biological analysis,[3, 4] 'radical traps' for transient radicals, and 'radical caps' in nitroxide mediated radical polymerization (NMRP). The reaction of transient carbon radicals with nitrones or nitroso compounds leads to persistent

nitroxides, which can readily be analyzed by EPR spectroscopy. Nitrones or nitroso compounds are therefore called 'spin traps.'[5, 6] These persistent nitroxide radicals are also incorporated into molecular magnets,[7, 8] organic batteries[9, 10] and other devices.[11] Additionally, the ability of nitroxides to be easily reduced to hydroxylamines has enabled their use as antioxidants in the study of cellular redox processes.[12] They have also been utilized as oxidizing agents (see Chapter 1) as in the well-known Anelli oxidation.[13] In analytical chemistry, nitroxides are used to detect nitric oxide,[14] and in the determination of the concentration of oxygen in biological systems.[15] Recently, the paramagnetic property of nitroxides has been utilized to quench fluorescence in the field of profluorescent nitroxides.

2.2 Nitroxides as Fluorescence Quenchers

Nitroxides are very effective at quenching fluorescence. This quality was first discovered by Stryer and Griffith in 1965.[16] When a nitroxide containing a 2,4-dinitrophenyl moiety was docked onto the strongly fluorescent anti-dinitrophenyl antibody protein, fluorescence emission of this protein was dramatically reduced. Reduced tumbling of the nitroxide complexed with the protein was indicated by broadening of the EPR signal. The potential of a nitroxide tethered to a fluorophore as potent probes of radical and redox states was realized in 1980s. Nitroxides were demonstrated to be efficient quenchers of excited singlet states of aromatic

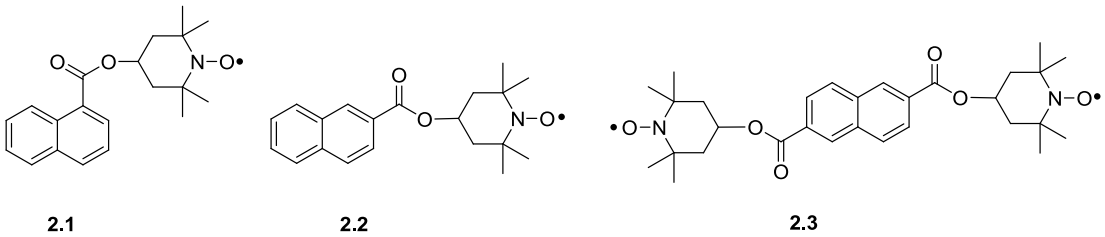
hydrocarbons.[17-22] In 1988 Blough and Simpson[23] illustrated a system in which the nitroxide is covalently linked to the fluorophore as shown in **Scheme 2.1**. As a 'profluorescent nitroxide', fluorescence emission of the fluorophore is quenched as a result of the proximity of the nitroxide. When the fluorophore-nitroxide complex is trapped by a radical to form a diamagnetic *N*-alkoxyamine or reduced to the corresponding hydroxylamine, the fluorescence is no longer quenched. As a result, fluorescence emission is restored.



Scheme 2.1 Representation of the tethering of a fluorophore to a nitroxide, which leads to fluorescence quenching. When chemical reactions convert the nitroxide to an *N*-alkoxyamine or hydroxylamine, the fluorescence emission is restored.

Blough and Simpson examined three different profluorescent nitroxides as shown in **Figure 2.2**; all have naphthalene derivatives as the fluorophore. They exhibited a 2.9 to 60-fold reduction in fluorescence quantum yield compared to the diamagnetic *O*-acylated analoques. Ascorbate reduction of dinitroxide **2.3** to the hydroxylamine resulted in a 10-fold increase in the fluorescence emission and a decrease in the EPR

signal. By following the rate of the fluorescence increase, the concentration of ascorbate could be conveniently and sensitively measured.



2.1 2.2 2.3

Figure 2.2 Profluorescent nitroxides containing naphthalene utilized in the 1988 study by Blough and Simpson

Fluorophore-nitroxide complexes have been described in the literature as profluorescent,[24] prefluorescent,[25-27] double spin and fluorescence sensors[28] or fluorophore-nitronyl probes.[29] In this review, all fluorophore-nitroxide couples will be referred to as profluorescent nitroxides. The use of profluorescent nitroxides as sensitive probes was reviewed recently by Bottle *et al*.[30] It should be noted that intermolecular processes also lead to effective fluorescence quenching. There are several publications on through-space fluorescence quenching of fluorophores by nitroxides, especially to elucidate the 3D structure of biomolecules.[31-34]

2.3 Mechanism of Quenching of Profluorescent Nitroxides

The fluorescence of nitroxide-fluorophore couples is quenched because of the ability of the nitroxide to quench both the excited singlet,[19, 35, 36] and triplet[21, 37]

states. The widely accepted mechanism is based on an electron spin exchange between the nitroxide species and the excited state fluorophore.[38] As shown in **Figure 2.3**, in a common process of fluorescence emission, an electron in the singlet ground state (S_0) of the fluorophore is excited by a photon to an excited singlet state (S_1 or S_2, etc.). The electron can return to the ground state in two steps. The first step involves loss of energy to the surrounding environment by vibrational relaxation and internal conversion (IC) until reaching the first excited singlet state (S_1). In the second step, internal conversion (IC) can occur to bring the electron back to the ground state (S_0) if the energy difference between the excited and the ground state is small. This process is radiationless. In the case of a large energy difference between S_1 and S_0 states, energy is lost by either the emission of a photon, called fluorescence, or by intersystem crossing (ISC) to the first triplet excited state (T_1) resulting in a change in spin multiplicity, following by the emission of a photon, known as phosphorescence. However in the later process, due to the long lifetime of the triplet state, the energy is usually lost in a non-radiative manner by interacting chemically or physically with the environment. As a result, if the rate of ISC is enhanced, the number of electrons to produce fluorescence from S_1 state is reduced, and therefore the fluorescence intensity decreases. This effect is applied to fluorescence quenching by the nitroxide. The interactions of the paramagnetic species are known to enhance the ISC process.[38]

When the unpaired spin of a nitroxide interacts with the electrons of a fluorophore, the electron spin of the fluorophore in the excited state (D_n) is exchanged with the electron spin of the nitroxide in the singly occupied molecular

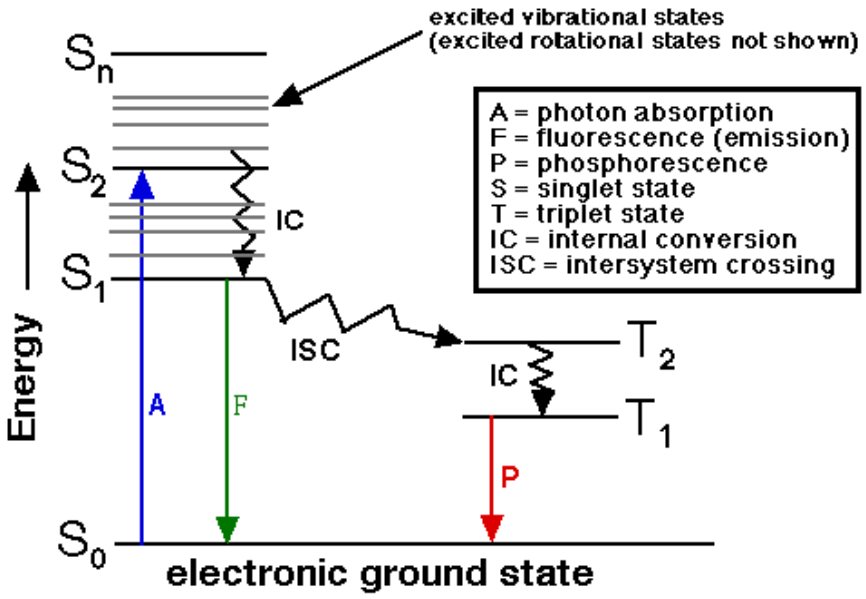


Figure 2.3 A Jablonski diagram of electronic transitions, adapted from http://www.shsu.edu/~chm_tgc/chemilumdir/JABLONSKI.html

orbital (SOMO) (**Figure 2.4**). As a consequence, the forbidden transitions from the S_1 to T_1 state (ISC) and subsequent T_1 to S_0 state are allowed, resulting in an increase in non-radiative processes, and a loss of fluorescence quantum yield. The extent to which fluorescence is quenched is related to the proximity of the nitroxide radical to the fluorophore. The greatest effect is observed when the distance is within 0-25 Å.[39]

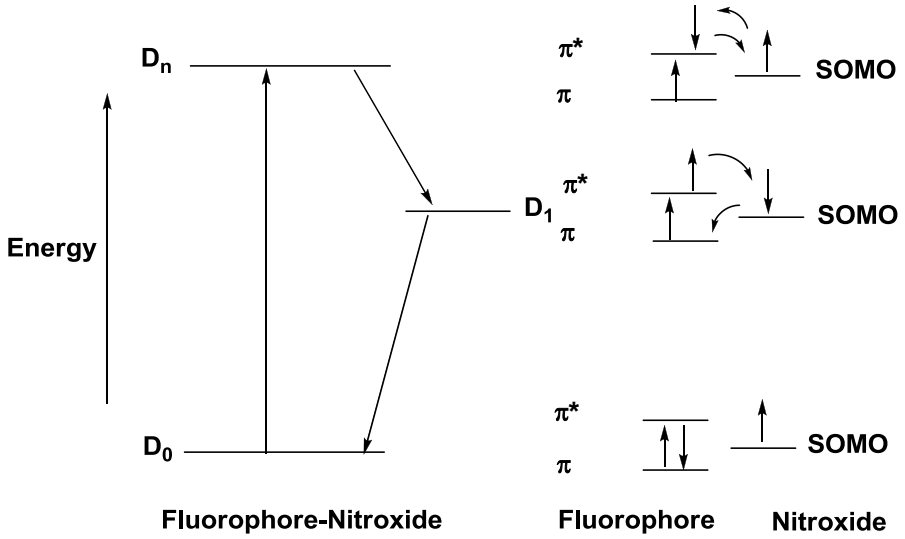


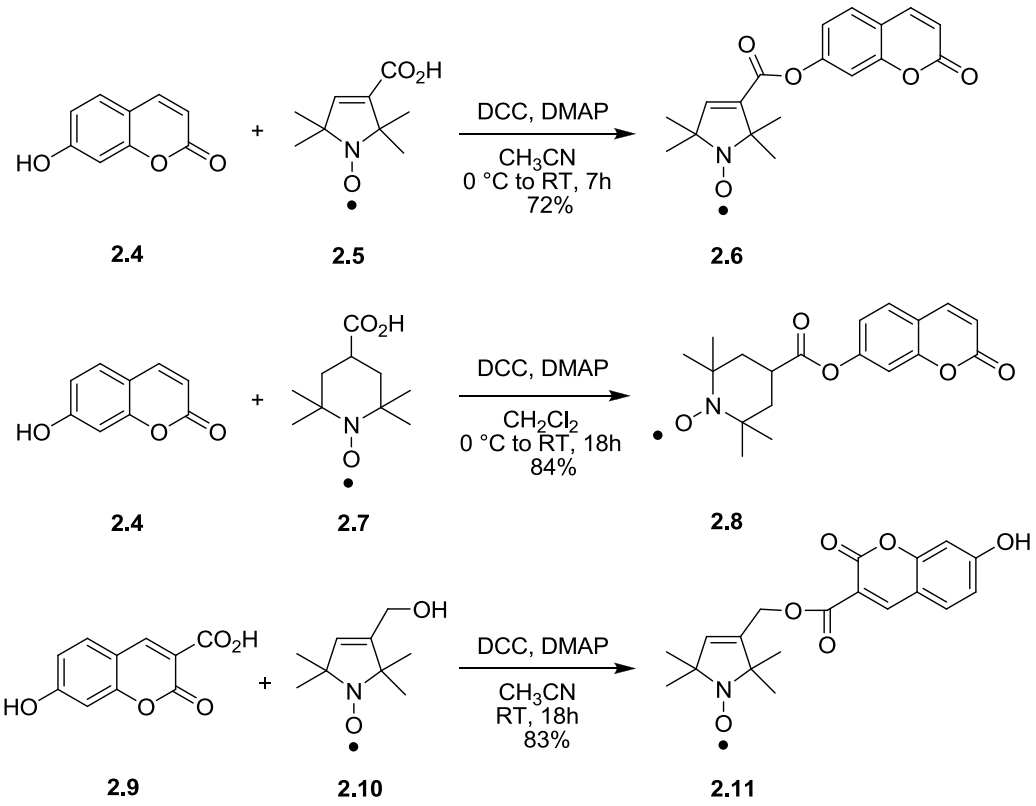
Figure 2.4 The electron spin exchange mechanism between a nitroxide and a fluorophore, adapted from Bottle *et al*.[30]

2.4 Synthesis of Profluorescent Nitroxides

2.4.1 Profluorescent Nitroxides with Ester, Amine, and Amide Linkages

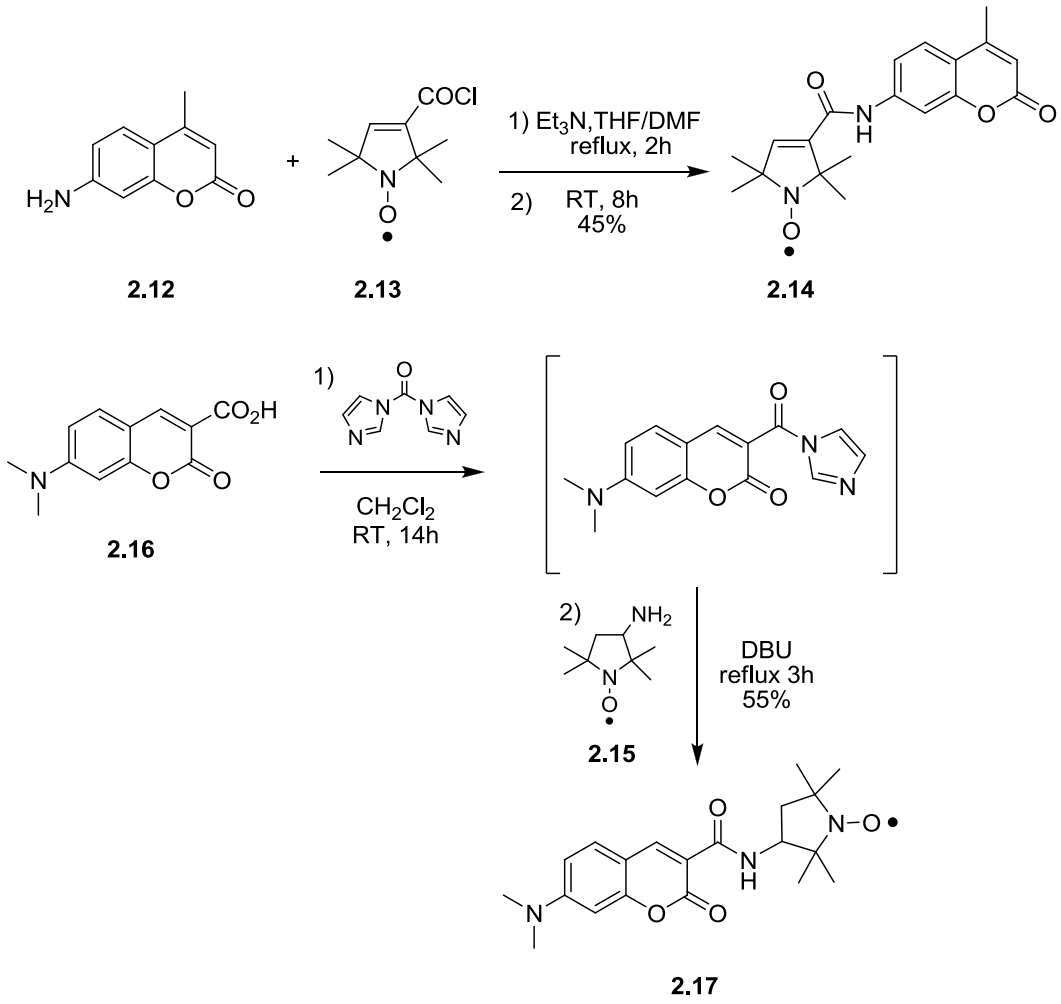
The most common way to synthesize profluorescent nitroxides is tethering commercially available piperidine based-nitroxides to fluorophores via ester, amine, or amide linkages. Examples of coumarin-nitroxides bearing ester or amide linkages have also been reported.[40-42] The synthesis of the ester linkage, as shown in **Scheme 2.2**, is carried out simply by the coupling of a 7-hydroxyl group of coumarin **2.4** and either carboxylic acid of pyrrolidine nitroxide **2.5** or of piperidine nitroxide **2.7**. Alternatively, the coupling of the 3-carboxylic acid of coumarin **2.9** with the hydroxyl group of pyrrolidine nitroxide **2.10**, using *N,N'*-dicyclohexylcarbodiimide (DCC) and

4-dimethylaminopyridine (DMAP) affords profluorescent nitroxides **2.6**, **2.8**, and **2.11** in good yields.[40]



Scheme 2.2 Sato's synthesis of coumarin profluorescent nitroxides bearing an ester linkage

Treatment of 7-amino-4-methyl coumarin **2.12** with nitroxide acid chloride **2.13** gave paramagnetic 7-aminocoumarin **2.14** with an amide linkage (**Scheme 2.3**), which exhibited an expected weak fluorescence at short wavelength (382 nm).[41] Nitroxide **2.14** was reduced to its hydroxylamine with Fe powder in acetic acid. Interestingly, the hydroxylamine has a similarly weak fluorescence. It was assumed



Scheme 2.3 Hideg's synthesis of 7-aminocoumarin **2.14** and 3-carboxy-7-dimethylaminocoumarin **2.17**

that the weak fluorescence of the hydroxylamine of **2.14** is due to diminished contribution of the nitrogen's lone pair into the fluorophore's conjugated system when the amide is formed. It has been reported that an amino or *N*,*N*-dialkylamino group enhances fluorescence of coumarin fluorophores.[43] Thus, an *N*,*N*-dimethyl coumarin profluorescent nitroxide was prepared by treating amine nitroxide **2.15**

with 3-carboxy-7-dimethylaminocoumarin imidazolide made *in situ* from coumarin **2.16** and 1,1'-carbonyldiimidazole (CDI), affording profluorescent nitroxide **2.17**. It exhibited a longer (460 nm) wavelength fluorescence emission compared to **2.14** and there was a 25-fold difference in the fluorescence intensities of the diamagnetic and paramagnetic forms.

Carboxylic acid derivatives of 3-hydroxy-4-methyl-2-quinoline,[44] acridine,[26] anthracene,[45, 46] pyrene[38, 47] and thioxanthonedioxide[48] (**Figure 2.5**) have been esterified with 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPOL) to form a variety of profluorescent nitroxides.

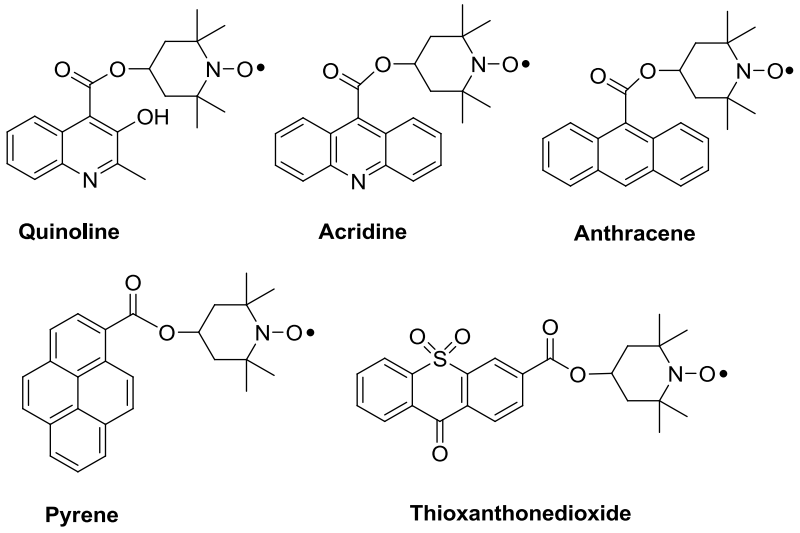
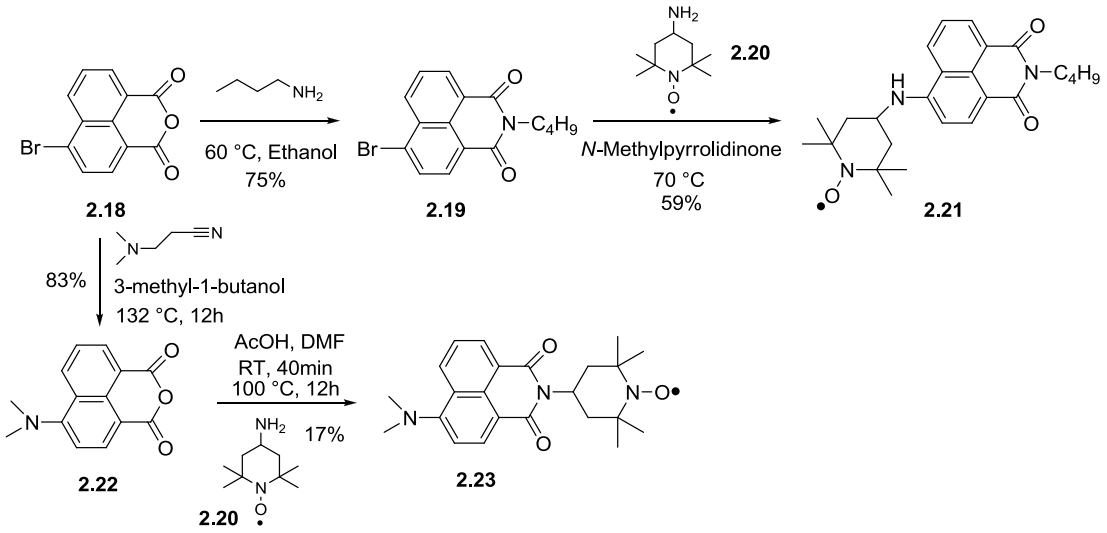


Figure 2.5 Structures of profluorescent nitroxides connected to fluorophores via an ester linkage

A number of substituted naphthalimides bearing a nitroxide on different positions have been prepared.[49-52] Electrophilic aromatic substitution was used to

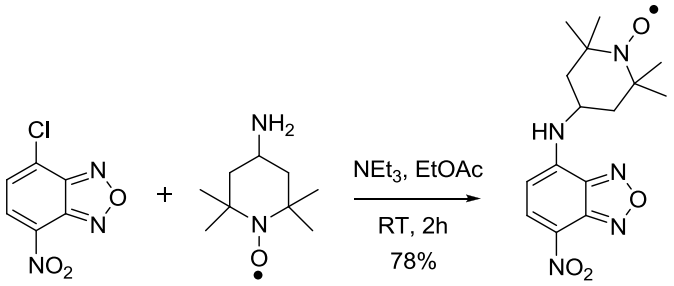
introduce 4-amino-2,2,6,6-tetramethylpiperidine (4-amino TEMPO) onto a naphthalene ring. Reaction of 4-bromo-1,8-naphthalic anhydride **2.18** with *n*-butylamine gave 4-bromo-*N*-butyl-1,8-naphthalimide **2.19** (**Scheme 2.4**).[49] 4-Bromo-*N*-butyl-1,8-naphthalimide **2.19** was then reacted with 4-amino TEMPO **2.20** to afford 1,8-naphthalimide profluorescent nitroxide **2.21**. Alternatively, 1,8-naphthalimide nitroxide **2.23** was prepared by substitution of 4-bromo-1,8-naphthalic anhydride **2.18** with 3-(dimethylamino)-propionitrile to give 4-dimethylamino-1,8-naphthalic anhydride **2.22**, following by reaction with 4-amino-TEMPO **2.20**.[53]



Scheme 2.4 Kollar's synthesis of 1,8-naphthalimide profluorescent nitroxides **2.21** and **2.23**

Another example of the formation of an amine linkage is reaction of 7-chloro-4-nitrobenzofurazan (NBD) **2.24** with 4-amino-TEMPO **2.20** in an aromatic

nucleophilic substitution reaction (**Scheme 2.5**) to yield NBD-nitroxide **2.25** with a weak yellow fluorescence: the 4-amino group of nitroxide is a part of the fluorophore.[41] The diamagnetic hydroxylamine of **2.25** showed about 33-fold increase of fluorescence intensity, probably because of the close vicinity of the donor and the acceptor.



Scheme 2.5 Hideg's synthesis of NBD-nitroxide **2.25**

The sulfonamide linkage on profluorescent nitroxides is usually formed via the reaction of dansyl chloride with an amine group on the corresponding nitroxide. Examples of piperidine- (**2.26**),[54] pyrrolidine- (**2.27**),[41, 55, 56] and nitronyl (**2.28**)[57, 58] profluorescent nitroxides with sulfonamide linkage are shown in **Figure 2.6**.

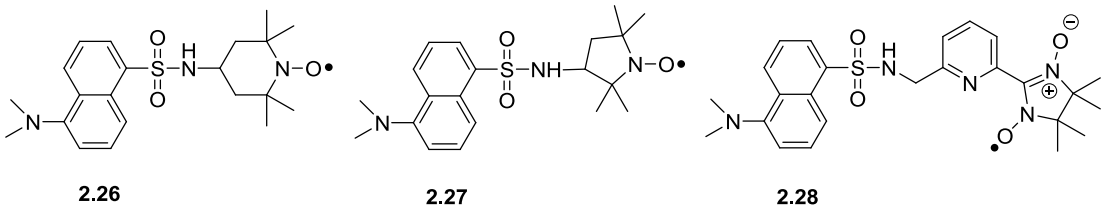
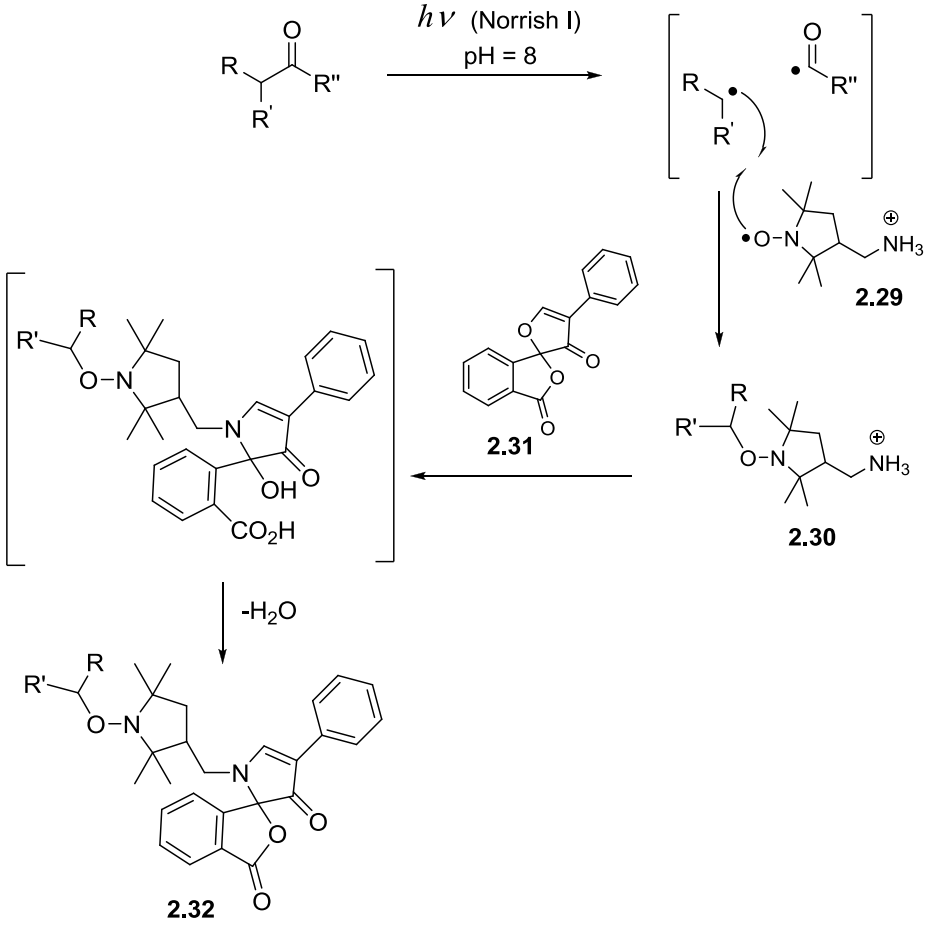


Figure 2.6 Dansyl-nitroxides tethered with a sulfonamide linkage

Although synthesis of profluorescent nitroxides via ester, amine, or amide linkage is convenient and results in high yield, Micallef *et al*.[24] suggested that the scission of these labile linkages may occur under harsh conditions, such as extreme heat and pH. These conditions might lead to the separation of nitroxide and the fluorophore, and consequently give an increase in the fluorescence as a false positive result. It should be noted that the nitroxide can also degrade upon treatment with excessive heat, strong acids, bases or redox agents, resulting in the interference of the expected fluorescence response of the profluorescent nitroxide. Blough *et al*.[59, 60] circumvented the problem of labile linkages within profluorescent nitroxides by a two-step trap-derivatization technique. This method was able to detect low levels of photochemically generated carbon-centered radicals in aqueous media.[61, 62] The analytes utilized in this study were ketones and α-keto acids, including α-ketovalerate, β-phenylpyruvate, β-hydroxypyruvate, α-ketocaproate, acetone, 3-pentanone, 3-methyl-2-butanone, 3-pinacolone and 2-hexanone in sodium borate buffer at pH = 8.0. As shown in **Scheme 2.6**, the carbon-centered radicals generated by Norrish I photolysis were trapped by 3-aminomethyl-2,2,5,5-tetramethyl-1-pyrrolidinyloxy free radical **2.29**. Alkoxyamine **2.30** was then coupled with fluorescamine **2.31**, which is not fluorescent. The resulting product **2.32** is highly fluorescent. This approach still has the drawback of requiring the trapped species **2.30** to be further derivatized with the fluorophore in a quantitative fashion.

This two-step procedure was initially employed to avoid the photolysis of the profluorescent nitroxide; however Scaiano *et al.*[63] successfully utilized a profluorescent nitroxide to monitor the formation of photo-generated benzyl radicals (*vide infra*).



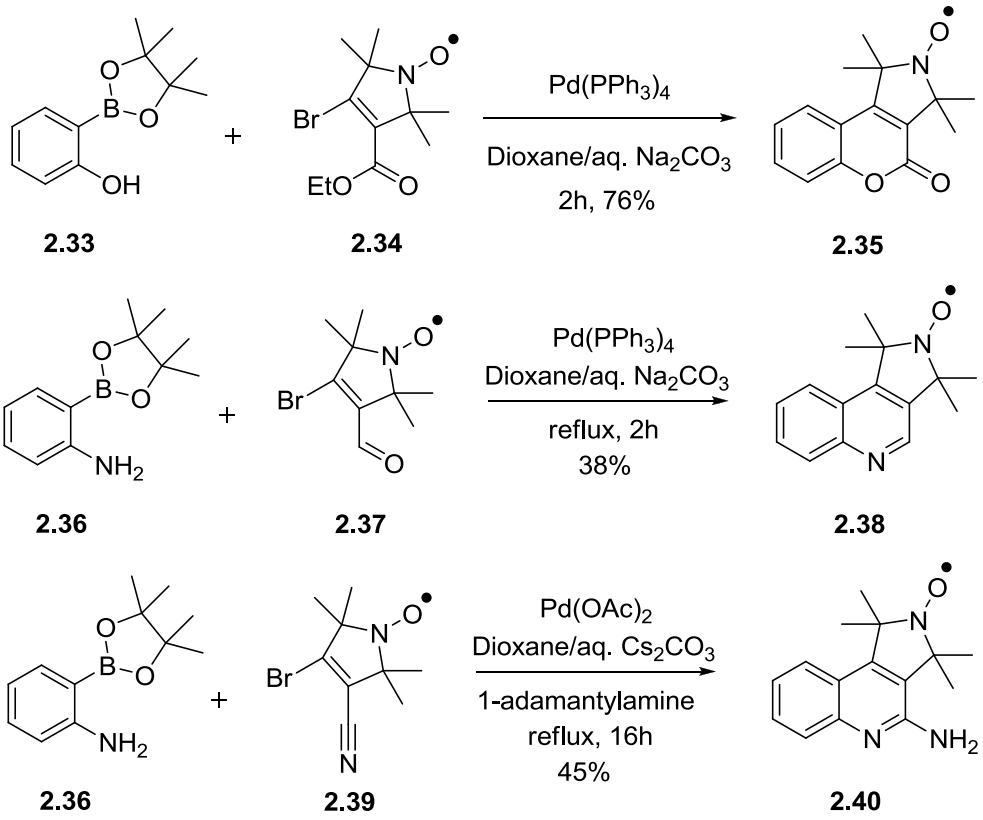
Scheme 2.6 Generation of radicals via Norrish I photolysis of ketones, followed by trapping with nitroxide **2.29**. The resulting alkoxyamine **2.30** was subsequently coupled with fluorescamine **2.31** to give the fluorescent compound **2.32**.

2.4.2 Profluorescent Nitroxides with Carbon-Carbon linkages

An alternative approach to avoid cleavage of the nitroxide from the fluorophore within profluorescent nitroxides is to use a robust all carbon framework, although the synthesis is sometime more challenging. Another advantage of using a carbon-carbon linkage is better fluorescence suppression. Generally, profluorescent nitroxides with a non-carbon linkage (ester, amide and sulfonamide) give 2-30 fold fluorescence enhancements when they are converted to diamagnetic derivatives.[46, 49, 64] However, fluorescence enhancements of 100-300 fold have been observed for all carbon linked profluorescent nitroxides.[65-68] It was shown that the greater enhancement is due to a higher quenching efficiency of the nitroxide. However, it is still not clear if this is because of the short distance between the nitroxide and the fluorophore, or the structural rigidity of the fused ring systems.

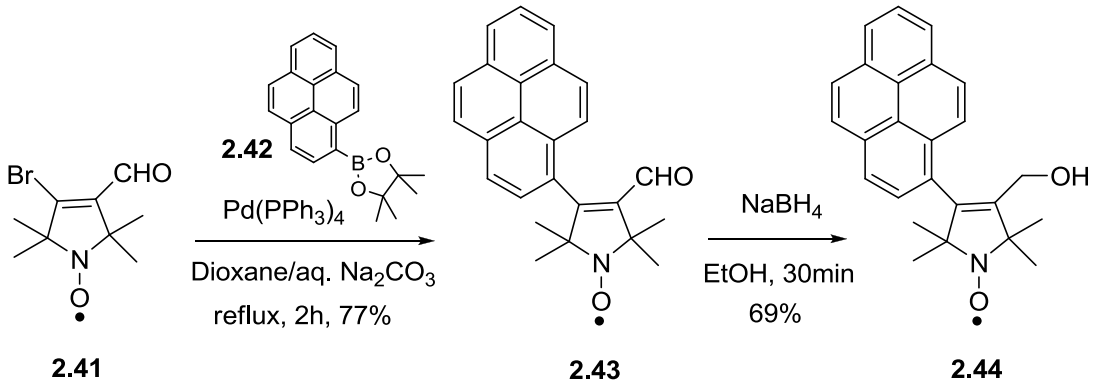
The common route to carbon-carbon linkages is palladium-catalyzed cross coupling reactions, including Suzuki,[66, 69-71] Sonogashira[67, 69] and Heck couplings.[65, 69] Examples using a Suzuki coupling to form profluorescent nitroxides under mild conditions are shown in **Scheme 2.7**. Reaction of pinacolate boronic ester **2.33** with pyrrolidine nitroxide bearing a β-bromo-α,β-unsaturated ester **2.34** effected Suzuki cross-coupling, followed by base-catalyzed lactonization to give the nitroxide-coumarin adduct **2.35**.[70] Similar conditions were used for the Suzuki coupling of pinacolate boronic ester **2.36** with aldehyde **2.37** or nitrile **2.39** to incorporate the

quinoline within profluorescent nitroxides **2.38** and **2.40**, respectively.



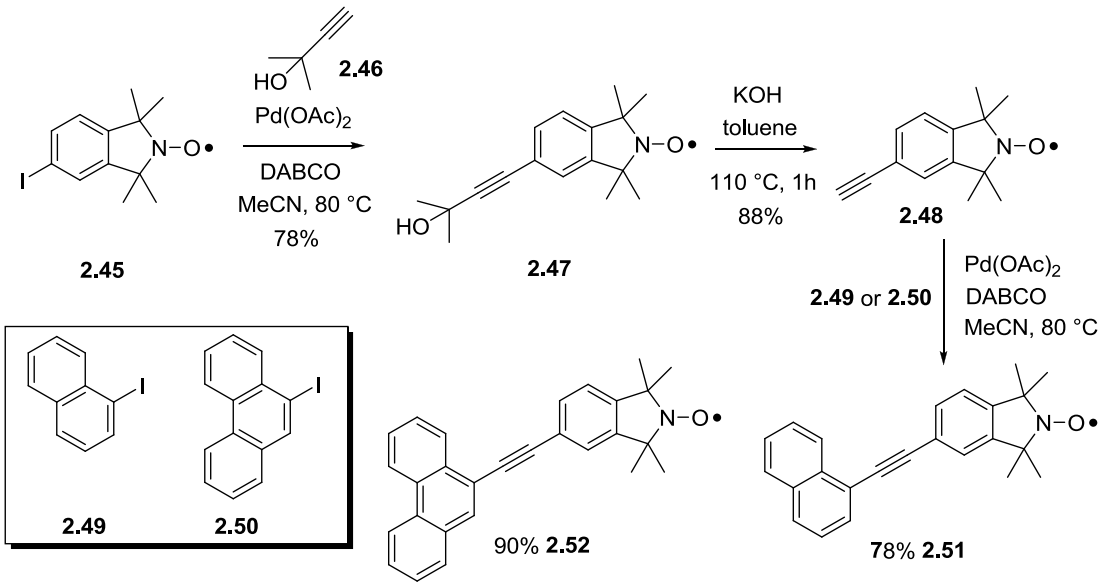
Scheme 2.7 Preparation by Hideg *et al*.[70] of coumarin derivative **2.35** and quinoline derivatives **2.38** and **2.40** utilizing Suzuki conditions

The long-lifetime pyrene fluorophore was also incorporated using a Suzuki cross-coupling as shown in **Scheme 2.8**. Pyrene bearing a 1-boronic ester **2.42** was reacted with β-bromo-α,β-unsaturated aldehyde **2.41** in the presence of $Pd(PPh_3)_4$ catalyst to give aldehyde **2.43**, which was reduced to alcohol **2.44** using sodium borohydride.[41]



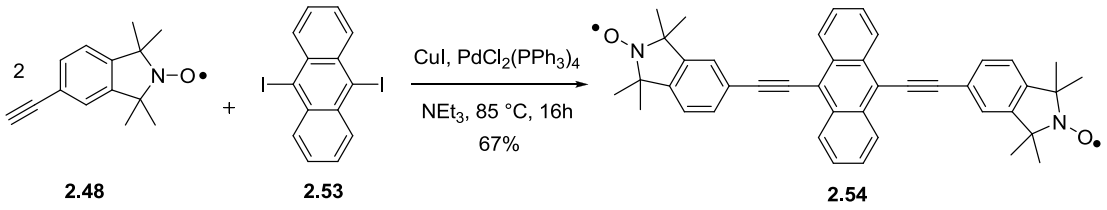
Scheme 2.8 Preparation by Hideg *et al*.[41] of pyrene derivatives **2.43** and **2.44** utilizing Suzuki coupling conditions

Bottle *et al*. have demonstrated the synthesis of mono- and di-isoindoline profluorescent nitroxides by Suzuki[66] and Sonogashira cross-couplings.[66, 67] Naphthalene,[67] phenanthrene,[67] and anthracene[66] were utilized as fluorophores. As shown in **Scheme 2.9**, iodoisoindoline nitroxide **2.45** was coupled to alkyne **2.46** under copper-free Sonogashira conditions to provide alkynyl isoindoline nitroxide **2.47**.[67] The terminal acetylene nitroxide **2.48** was obtained by treating isoindoline **2.47** with KOH. Sonogashira coupling of isoindoline **2.48** with 1-iodonaphthalene **2.49** or 1-iodophenanthrene **2.51** gave profluorescent isoindoline nitroxides **2.51** and **2.52** in 78% and 90% yield, respectively.



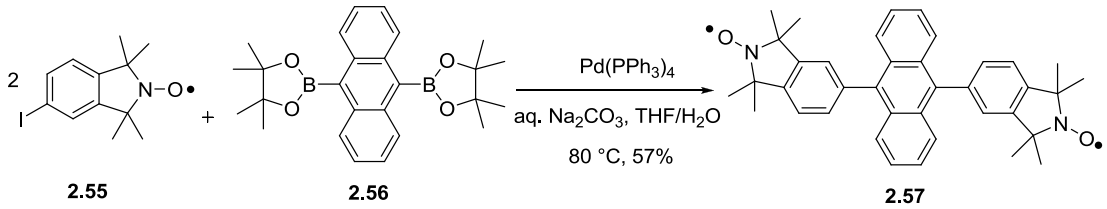
Scheme 2.9 Bottle's synthesis of profluorescent isoindoline nitroxides **2.51** and **2.52** using copper-free Sonogashira cross-coupling

Bottle extended this methodology to prepare bis-isoindoline profluorescent nitroxide **2.54** from 9,10-diiodoanthracene **2.53**, however the reaction resulted in a low yield under copper-free Sonogashira cross-coupling.[66] The product was obtained in a good yield after switching to standard Sonogashira conditions and the use of the acetylene nitroxide **2.48** in excess, as shown in **Scheme 2.10**.



Scheme 2.10 Bottle's synthesis of bis-isoindoline profluorescent nitroxide **2.54** using standard Sonogashira cross-coupling

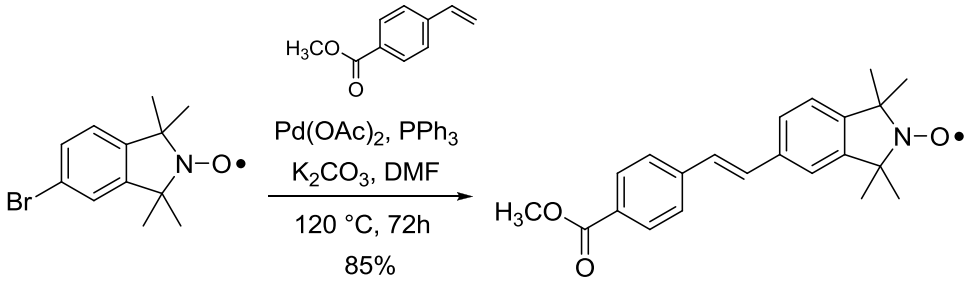
Synthesis of a similar bis-isoindoline nitroxide **2.57** attempted under Suzuki-Miyaura cross-coupling resulted in a low yield. Using standard Suzuki conditions, iodoisoindoline **2.55** was coupled to bis-pinacolate boronic ester **2.56** to give bis-isoindoline profluorescent nitroxide **2.57** in 57% yield (**Scheme 2.11**).[66]



2.55 **2.56** **2.57**

Scheme 2.11 Bottle's synthesis of bis-isoindoline profluorescent nitroxides **2.57** using a standard Suzuki cross-coupling

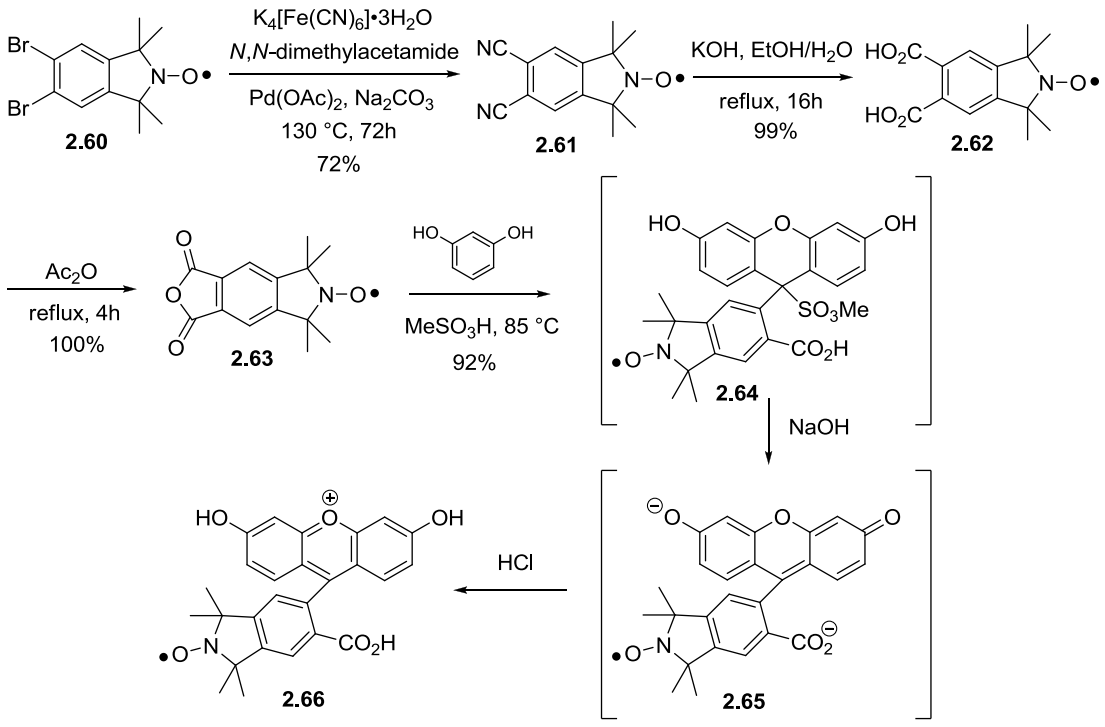
The synthesis of profluorescent isoindoline nitroxides via palladium-catalyzed Heck alkenylation was also reported.[65] The reaction of bromoisoindoline nitroxide **2.58** with methyl 4-vinylbenzoate in the presence of a palladium catalyst gave the highly conjugated acrylate substituted isoindoline nitroxide **2.59** in good yield (**Scheme 2.12**).



2.58 **2.59**

Scheme 2.12 Bottle's synthesis of isoindoline nitroxide **2.59** via a Heck coupling reaction

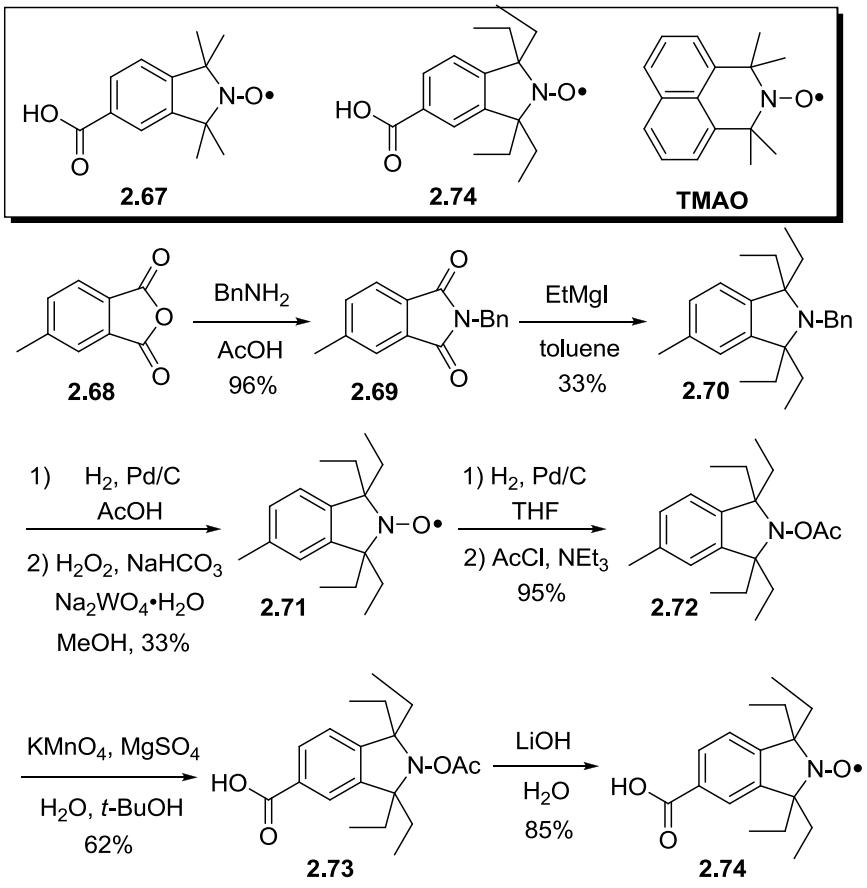
Beside metal-catalyzed cross-coupling reactions, profluorescent nitroxides with carbon-carbon linkages have be synthesized by simple condensations. The synthesis of fluorescein is commonly achieved via the condensation of a substituted phthalic anhydride with two equivalents of resorcinol. To incorporate the nitroxide functionality within the fluorescein structure, a nitroxide-based phthalic anhydride **2.63** was synthesized and used as a direct precursor to the final profluorescent nitroxide, as shown in **Scheme 2.13**.[72] The nitroxide anhydride **2.63** was obtained by cyanation of the dibromo nitroxide **2.60**, followed by hydrolysis of dicyano nitroxide **2.61** to give the dicarboxy derivative **2.62**. Subsequent cyclization in acetic anhydride afforded the nitroxide-fused phthalic anhydride **2.63**. Two equivalents of resorcinol were then combined with **2.63** in methanesulfonic acid to give the sulfonate ester intermediate **2.64**, which was subsequently treated with NaOH to produce the fluorescein dianion **2.65**. For ease of purification and handling, isolation of the final product was achieved by acidification to precipitate the fluorescein nitroxide **2.66**. In aqueous solutions, fluorescein derivatives exist in cationic, neutral, anionic, and dianionic forms. Conversion between these species is dependent on the pH of the aqueous solution.



Scheme 2.13 Bottle's synthesis of the pH-dependent fluorescein isoindoline nitroxide **2.66**

Bottle *et al*.[73] have shown that water soluble carboxylic acid isoindoline nitroxide **2.67** is the most effective nitroxide for scavenging the species generated from radiation-induced oxidative stress in cells. In an effort to synthesize a nitroxide that would be less prone to simple *in vivo* reduction, isoindoline nitroxide **2.74** containing the bulky geminal ethyl groups was designed.[74] 4-Methylphthalic anhydride **2.68** was condensed with benzylamine to give 2-benzyl-4-methylphthalimide **2.69** in excellent yield (**Scheme 2.14**). Phthalimide **2.69** was treated with six equivalents of ethylmagnesium iodide to give tetraethylisoindoline

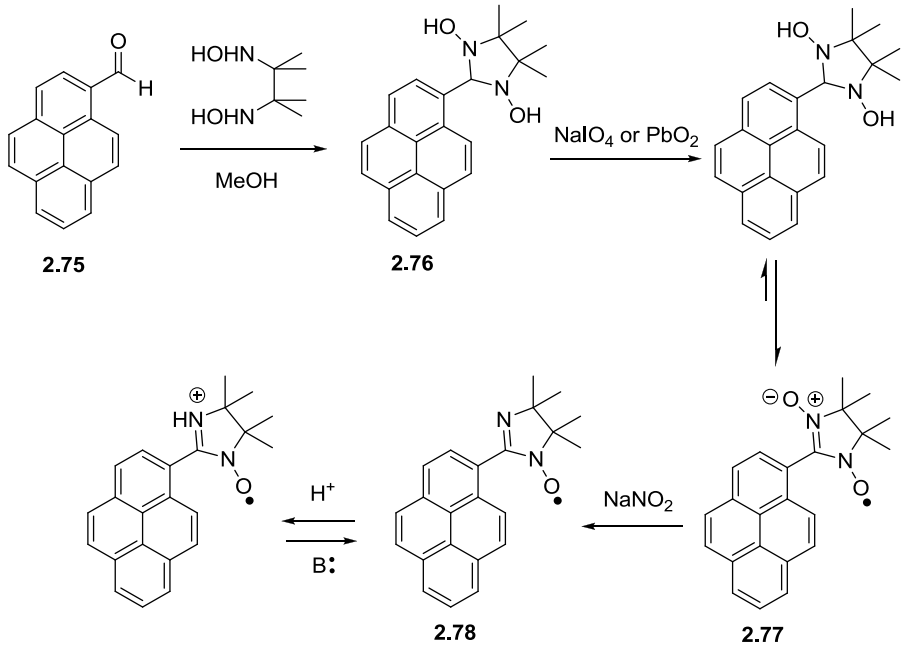
2.70 in modest yield. Deprotection of the benzyl group under reductive conditions following by oxidation with hydrogen peroxide and sodium tungstate provided isoindoine nitroxide **2.71**. Reduction of **2.71** with hydrogen and palladium over carbon following by protection of the hydroxylamine using acetyl chloride gave *N*-acetate **2.72**. Permaganate oxidation of the benzylic methyl carbon provided benzoic acid **2.73**. Hydrolysis of the acetate group by lithium hydroxide, following by oxidation in air afforded the isoindoline nitroxide **2.74**. A similar synthetic route was



Scheme 2.14 Synthesis of isoindoline nitroxide **2.74** for cellular redox process

reported to make 1,1,3,3-tetramethyl-2,3-dihydro-2-azaphenalene-2-yloxyl, which the Bottle group has given the acronym TMAO (**Scheme 2.14**).[68] Recently, fluorescein isoindoline nitroxide containing the bulky geminal ethyl groups has been shown to be a good candidate as a two-photon fluorescent oxidative stress indicator in Chinese hamster ovary (CHO) cells, and has low cytotoxicity toward these cells.[75]

Wang *et al*.[76, 77] reported the synthesis of pyrene nitronyl nitroxide **2.77** and 1-pyrene imino nitroxide **2.78** as a proton-sensitive fluorescent switch. Pyrenecarboxaldehyde **2.75** reacted with 2,3-dimethyl-2,3-bis(hydroxylamino)-butane to give di(hydroxylamine) **2.76** (**Scheme 2.15**). The nitronyl nitroxide **2.77** was

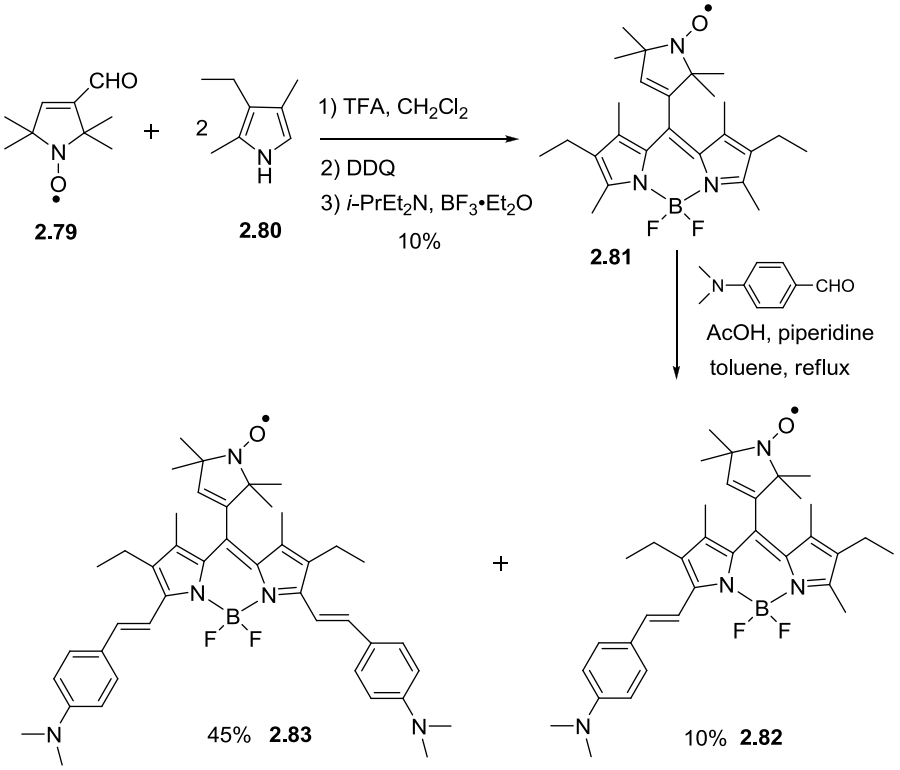


Scheme 2.15 Wang's synthesis of pyrene nitronyl nitroxide **2.77** and 1-pyrene imino nitroxide **2.78**

reduced to provide 1-imino nitroxide **2.78**. The fluorescence of pyrene in 1-imino nitroxide **2.78** is strongly quenched because of the presence of both the nitroxide radical and the imino lone pair. Protonation of the imino group retards the quenching because the lone pair electrons on nitrogen are no longer available to quench the fluorescence.

Profluorescent nitroxides were synthesized based on three different fluorophores emitting long wavelengths between 610 and 800 nm containing: boron-dipyrromethene (BODIPY) dye, NileRed and Ru-complex.[78] The lower energy required for the excitation of these fluorophores makes these well suited for biological applications. Among these fluorophore-nitroxide adducts, **2.83** exhibited the highest sensitivity to sodium ascorbate. For the synthesis of these BODIPY derivatives, a mixture of paramagnetic aldehyde **2.79** and 2,4-dimethyl-3-ethylpyrrole **2.80** was treated with catalytic trifluoroacetic acid (TFA) followed by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), isopropylethylamine and boron trifluoride diethyl etherate to give compound **2.81** (**Scheme 2.16**). The emission wavelength of **2.81** in MeOH is in the shorter wavelength region (558 nm), and the Stokes shift is also small (23 nm). To extend the conjugation, and thus shift both the excitation and emission towards a longer wavelength, **2.81** was condensed with 4-(*N*,*N*′-dimethylamino)benzaldehyde in the presence of catalytic acetic acid and piperidine under azeotropic removal of water

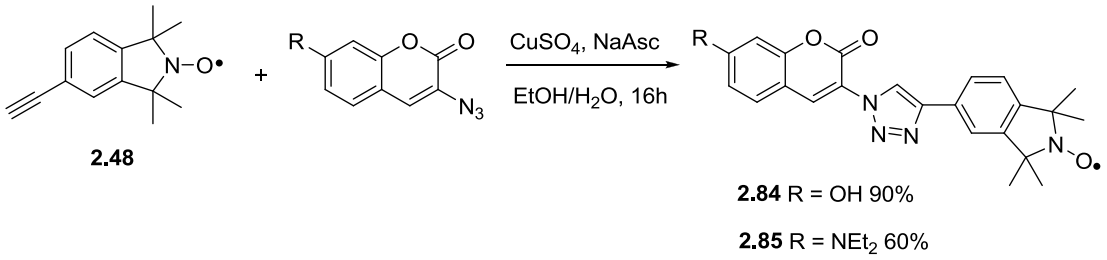
to give a mixture of the 3-monostyryl derivative **2.82** and 3,5-distyryl **2.83**. Nitroxides **2.82** and **2.83** both exhibited long emissions in MeOH: 695 nm and 785 nm, and the Stokes shifts are 66 nm, and 55 nm, respectively.



Scheme 2.16 Hideg's synthesis of long wavelength emitting-BODIPY nitroxides **2.82** and **2.83**

Recently profluorescent nitroxides bearing a triazole linker between a coumarin fluorophore and an isoindoline nitroxide were prepared in good yields using the copper catalyzed azide-alkyne 1,3-dipolar cycloaddition ("click") reaction on alkynyl nitroxide **2.48** (**Scheme 2.17**).[79] Nitroxides containing 7-hydroxy **2.84** and 7-diethylamino **2.85** substitutions on their coumarin rings displayed significant

fluorescence suppression. This work indicates that the triazole subunit is an excellent linker as it allows the quenching effect to be transferred from the nitroxide to the fluorophore by extending the conjugated system.

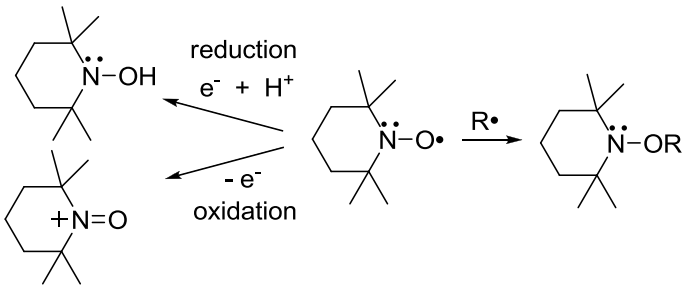


Scheme 2.17 Synthesis of coumarin isoindoline nitroxides **2.84** and **2.85** via "click" reaction

2.5 Applications of Profluorescent Nitroxides

Nitroxides are easily reduced to the corresponding hydroxylamines, or oxidized to oxoammonium cations. Nitroxides also efficiently trap carbon radicals, as shown in **Scheme 2.18**. These properties have given rise to a variety of applications of proflurescent nitroxides as probes for redox changes and radical trapping. Likhtenstein[38] illustrated the most important applications of fluorescent nitroxides as follows: (1) the ability to use both fluorescence and EPR properties of the probe to obtain space and temporal information from the same specific part of a system under interest; (2) investigate micropolarity and molecular dynamics of media in the fluorophore region by fluorescence and in the nitroxide region by EPR; (3) monitor redox and spin trapping processes in systems of any optical density by EPR, or by

fluorescence in systems of low optical density; (4) construct a variety of organic profluorescent nitroxides with photo-functionality; (5) analyze metal ions using fluorescence and EPR techniques; (6) explore mechanisms of intramolecular photochemical and photophysical processes.



Scheme 2.18 Three main reactions of dialkyl nitroxides: reduction, oxidation and trapping carbon radicals

2.5.1 Probes for Redox Changes

One-electron reduction of nitroxides to form the corresponding hydroxylamine deriverives is the most widely utilized reaction in the application of profluorescent nitroxide probes to biological systems. Naturally occurring antioxidants which are used to control oxidative stress including ascorbate, tocopherol, uric acid, serum albumin and glutathione can reduce the profluorescent nitroxide to the hydroxylamine, resulting in the recovery of the fluorescence. The sensitivity of profluorescent nitroxides towards ascorbate has been well documented. Blough and Simpson were the first to show that ascorbic acid can be detected in this way using naphthalene-nitroxide probes, as shown in **Figure 2.2**

(*vide supra*). Lozinsky *et al*.[54] employed reaction between dansyl-nitroxide probe **2.26** and sodium ascorbate to generate a calibration curve by varying the concentration of ascorbate. This probe was successfully applied to the measurement of ascorbic acid in several fruit juice samples. When commercially purchased fruit juices were examined, ascorbic acid concentrations were close to those claimed by the manufacturer. Without preservatives in fruit juices, ascorbic acid was not preserved (**Figure 2.7**, **I** *vs* **II** and **III** *vs* **IV**). Ascorbic acid concentration in freshly squeezed orange was found to be high and did not change after 24 hours (**Figure 2.7 V**).

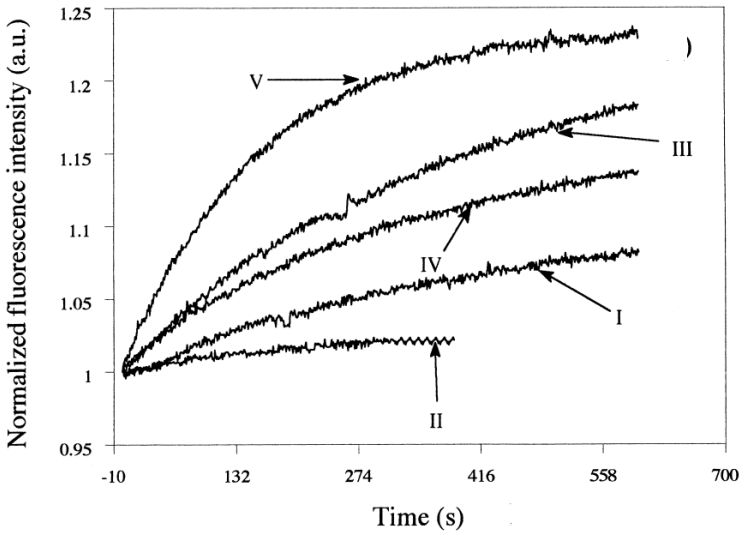
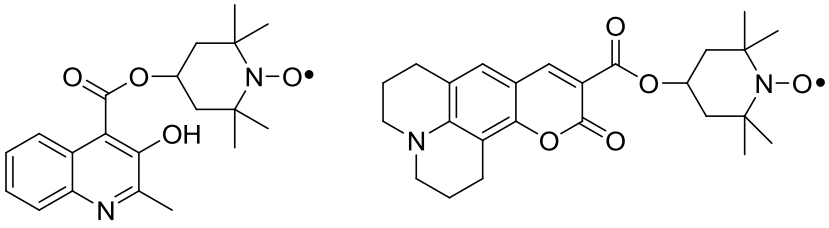


Figure 2.7 Enhancement of fluorescence caused by ascorbic acid contained in natural fruit juices. **(I)** Peach nectar without preservatives just opened (diluted); **(II)** peach nectar without preservatives after 24h (diluted); **(III)** lemon juice with preservatives just opened (diluted); **(IV)** lemon juice after storing for 24h in air (diluted); **(V)** natural juice squeezed from fresh oranges after 24h (diluted). Adapted from Lozinsky *et al*.[54]

This work was extended to biological systems, where it was shown that the rate of reaction between dansyl-nitroxide **2.26** and ascorbate increased with increasing protein concentrations, because of the adsorption of the ascorbate and the nitroxide onto the protein.[80] As a result of this study, in order to get the accurate quantitative information to determine antioxidant properties of complex biological samples, nitroxide reduction rates have to be compared to a similar system. This approach was applied to the analysis of the antioxidant capacity in whole-blood samples[81] and human serum albumin (HSA).[82] For example, quinoline-nitroxide **2.86** and coumarin-nitroxide **2.87** (**Figure 2.8**) were selected to explore the reducing capacity of three different antioxidants, ascorbic acid, Trolox and caffeic acid. These profluorescent nitroxide probes were anchored into HSA, a fatty acid



2.86 **2.87**

Figure 2.8 Quinoline-nitroxide **2.86** and coumarin-nitroxide **2.87** utilized to explore capacity of antioxidants by Aspée *et al*.[82]

transport protein in blood plasma. Association constants of **2.86** (9.0×10^4 M^{-1}) and **2.87** (5.0×10^4 M^{-1}) were evaluated based on the tryptophan (W214) residue fluorescence quenching by nitroxide probes. The addition of HSA to **2.87** induced a

hypsochromic shift of the absorbance and fluorescence spectra, indicating a relatively hydrophobic environment for **2.87** adsorbed onto the HSA. In order to mimic the repair of oxidative radical damage in the enzyme, profluorescent nitroxide **2.87** was treated with several different reducing agents to probe the efficacy of their radical scavenging. Addition of ascorbic acid increases the fluorescence intensity of coumarin-nitroxide **2.87** as shown in **Figure 2.9 (A)**. Rate constants (k_{HSA}) of nitroxide reduction in the presence of HSA were calculated from the pseudo first order kinetic plots (**Figure 2.9 (B)**) and **Equation 2.1**, where X is the molar fraction of the nitroxide probe in buffer and HSA, k_{buffer} is the rate constant in buffer only, and $k_{HSA,app}$ is the apparent rate constant in HSA and buffer.

Ascorbic acid was the most effective antioxidant at reducing the nitroxide, both in buffer and when bound to the enzyme, followed by Trolox and caffeic acid. However, the ratio between the rate constant in HSA and buffer clearly showed that ascorbic acid was impeded in reacting with nitroxide probes **2.86** and **2.87** located in a hydrophobic environment of the protein (k_{HSA}/k_{buffer} = 0.8 and 0.76 for **2.86** and **2.87**, respectively). Larger rate constant ratios were observed for Trolox in HSA with k_{HSA}/k_{buffer} = 1.9 and 1.6 for **2.86** and **2.87**, respectively. This suggests that hydrophobicity plays a role in the efficacy of reaction in this system.

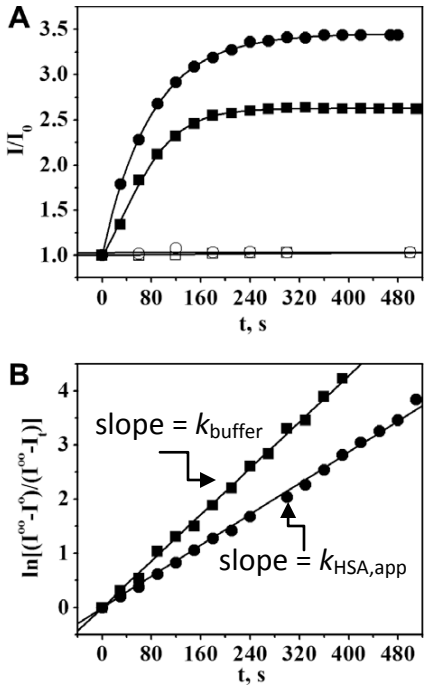


Figure 2.9 (A) Fluorescence profile of **2.87** (2.5 μM, λmax=490 nm) in phosphate buffer, pH 7.0 (■), and in HSA (●) after addition of 1 mM ascorbic acid. (B) Pseudo first order kinetics, adapted from Aspée *et al*.[82]

$$k_{\mathrm{HSA,app}} = k_{\mathrm{buffer}} \cdot X_{\mathrm{buffer}} + k_{\mathrm{HSA}} \cdot X_{\mathrm{HSA}} \qquad \textbf{Equation 2.1}$$

Profluorescent nitroxides incorporating a polymethine-cyanine fluorophore emitting at 568 (**2.88**) and 661 (**2.89**) nm also displayed sensitivity to ascorbate as a reductant (**Figure 2.10**).[83] These hybrid compounds are suitable to be used to visualize reducing species or radicals *in vivo* because less energy is required to excite the fluorophores, resulting in less cell damage. The reduction of the five membered-ring pyrene nitronyl nitroxide **2.77** with the antioxidants ascorbate, quercetin and galangin was demonstrated by Likhtenshtein *et al*.[29] This study also showed that the

fluorescence of pyrene nitronyl nitroxide **2.77** was turned on by the biologically important superoxide radical generated by the xanthine/oxidase system (XOS). The authors claim that the reaction between pyrene nitronyl nitroxide **2.77** and superoxide occurs via nitroxide reduction to the hydroxylamine. A superoxide flux as low as 10 nM/min was detected using this approach.

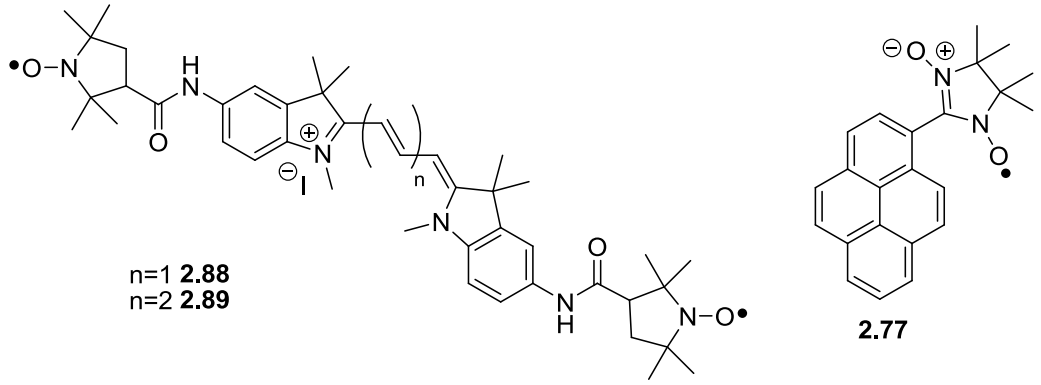
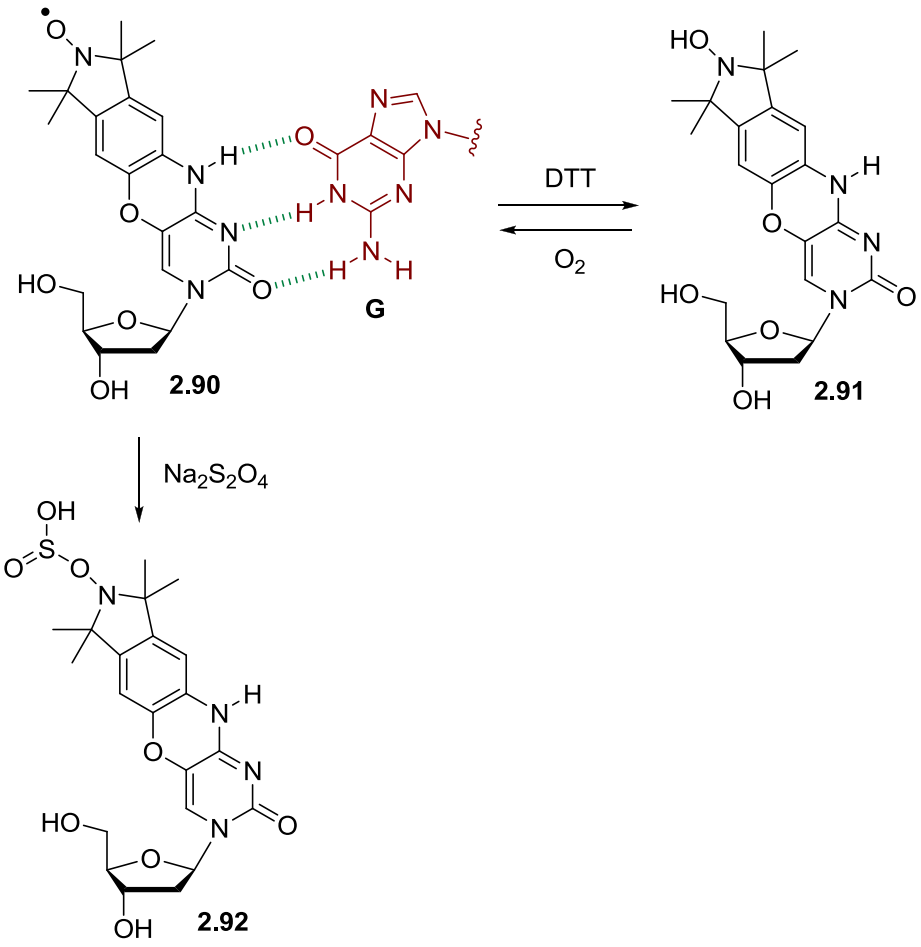


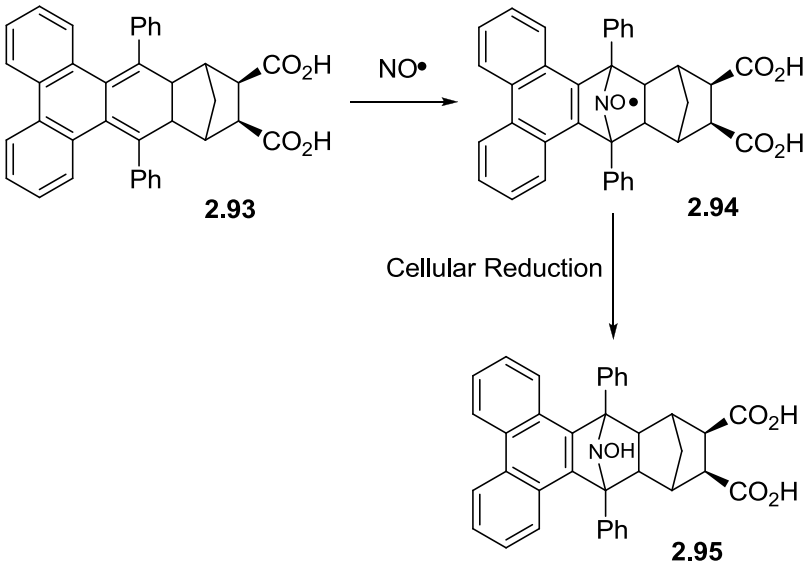
Figure 2.10 Profluorescent nitroxides utilized in probing biological redox processes

The isoindoline nitroxide **2.90**[84] attached to a fluorescent nucleoside, where a substituent on the terminal aromatic ring can form hydrogen bonds to base-pair with guanine (**G**) (**Scheme 2.19**) was incorporated into nucleic acids to study the structure and stacking of the DNA helix.[85] The nucleoside becomes fluorescent upon reduction of the nitroxide with a mild reducing agent, dithiothreitol (DTT) or sodium dithionite, or as well as by normal cellular redox processes. Hydroxylamine **2.91** was readily oxidized back to the nitroxide upon exposure to oxygen, whereas the sulfurous ester **2.92** was not affected by incubation with oxygen.



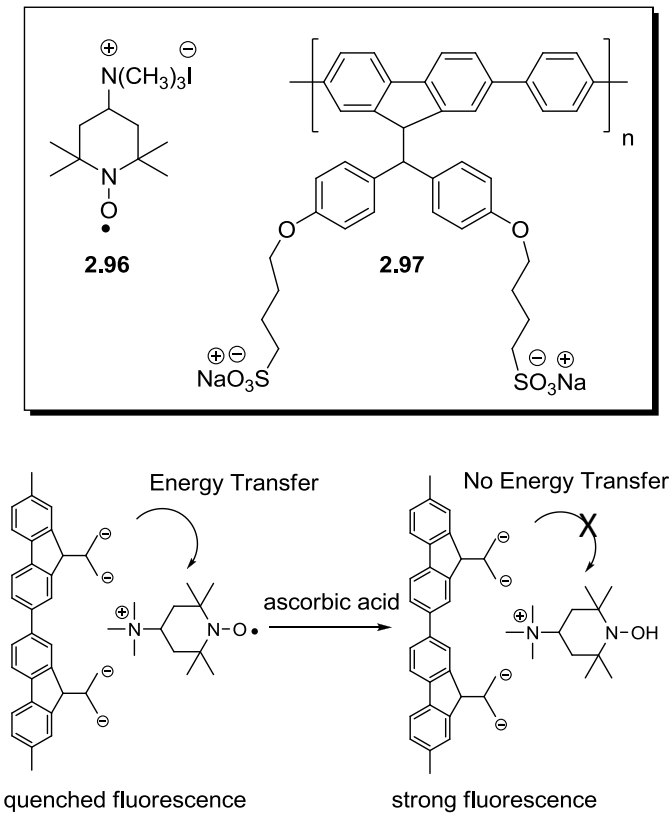
Scheme 2.19 Reduction and trapping of base-pairing isoindoline nitroxide **2.90**

Sustman *et al.*[86-88] demonstrated that a precursor to a nitroxide can be utilized in cellular systems for the detection of nitric oxide. The cheletropic trap **2.93**[87] reacted with nitric oxide, generating the profluorescent nitroxide **2.94** *in situ* in the cell, as shown in **Scheme 2.20**. Nitroxide **2.94** was then metabolically reduced to form the fluorescent hydroxylamine **2.95** in the cellular environment.



Scheme 2.20 Reaction of a cheletropic trap with nitric oxide to form profluorescent nitroxide **2.94**; subsequent reduction formed fluorescent hydroxylamine **2.95**.

Besides covalent bonding, nitroxides can be complexed with a fluorophore via electrostatic ionic attractions.[89] The cationic nitroxide **2.96** adheres to the fluorescent anionic polymer **2.97** through electrostatic interactions, resulting in fluorescence quenching (**Scheme 2.21** and **Figure 2.11 (2)**). When a solution of ascorbic acid was added to the system, an intense increase in fluorescence was observed (**Figure 2.11 (3)**). This complex was found to be selective with ascorbic acid. It was found that dissolved oxygen quenched roughly half of the fluorescence (**Figure 2.11 (1)**). When nitrogen was bubbled through the original solution of the polymer, the fluorescence intensity increased about 100% due to the purging of dissolved oxygen (**Figure 2.11 (4)**).



Scheme 2.21 Structures of cationic nitroxide **2.96** and conjugated anionic polymer **2.97** used by Wang *et al*,[89] and schematic representation of the antioxidant probe

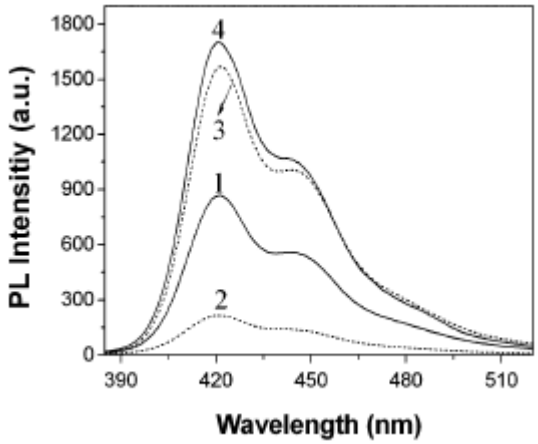


Figure 2.11 Fluorescence emission of polymer **2.97**: (1) exposed to air, (2) after addition of nitroxide **2.96**, (3) with nitroxide **2.96** and ascorbic acid, (4) under N_2, adapted from Wang *et al*.[89]

A commercially available acridine-profluorescent nitroxide **2.98** from Molecular Probes, Inc. (**Figure 2.12**) has been used in the detection of reactive oxygen species (ROS) in biological systems. The mechanism is again assumed to be due to nitroxide reduction to form a highly fluorescent hydroxylamine.[90-92] The ester derivative **2.99** was also utilized to detect peptide and protein-based radicals.[26] For a model study of peptide-based radicals, *N*-acetyl-L-tyrosineamide was oxidized by hydrogen peroxide, and catalyzed by horseradish peroxidase. Trapping of the nitroxide **2.99** by the generated radicals resulted in an increase of the fluorescence emission. Hydrogen transfer from photo-induced enols of dibenzoylmethane and avobenzene,[93] as well as a variety of phenolic compounds[94, 95] to profluorescent nitroxide **2.87** was demonstrated to evaluate antioxidant efficacy.

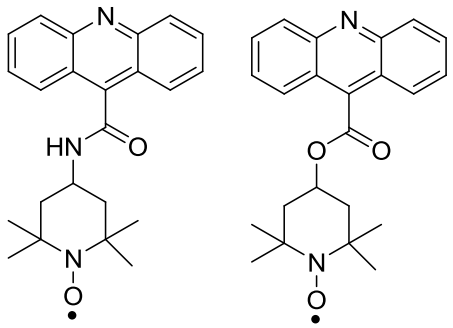
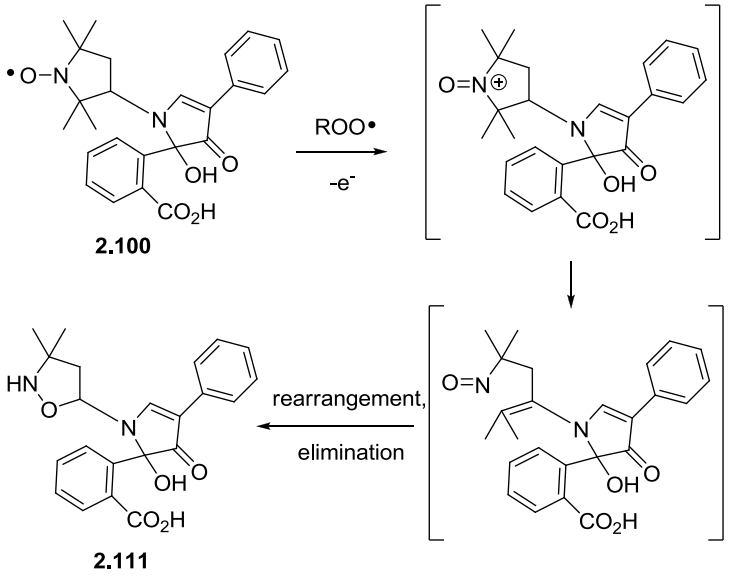


Figure 2.12 Commercially available acridine-profluorescent nitroxides **2.98** and **2.99**

In addition to reduction, oxidation of nitroxides to oxoammonium ions also serves to recover the fluorescence emission of profluorescent nitroxides, but this

strategy is not very common. One example by Blough *et al*.[96] described irreversible oxidation of fluorescamine derivatized nitroxide **2.100** to the oxoammonium cation by peroxyl radicals and other radical oxidants, following by ring cleavage of oxoammonium cation and rearrangement to generate the highly fluorescent diamagnetic product **2.111** (**Scheme 2.22**). The mechanism of the elimination step to give **2.111** was unknown.

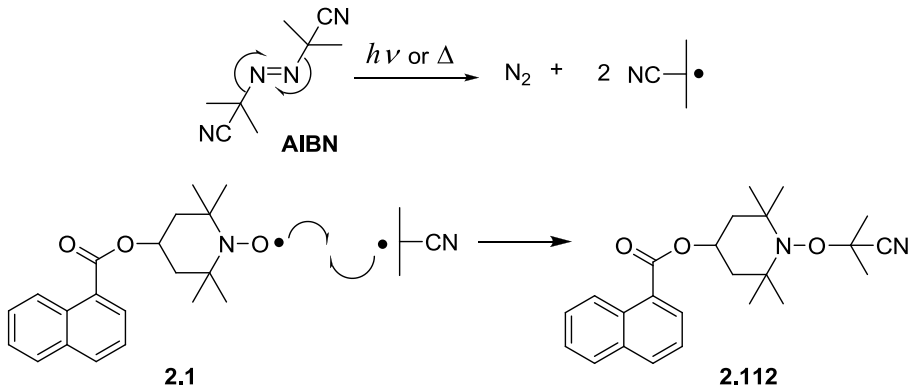


Scheme 2.22 Oxidation followed by decomposition of profluorescent nitroxide **2.100** to form fluorescent product **2.111**

2.5.2 Probes for Radical Trapping

Nitroxides trap carbon at near-diffusion rate constants (10^7-10^9 $M^{-1}s^{-1}$),[97] converting organic radicals to diamagnetic alkoxyamines. Blough *et al*.[98, 99] was the first to utilize profluorescent nitroxides for trapping experiments.

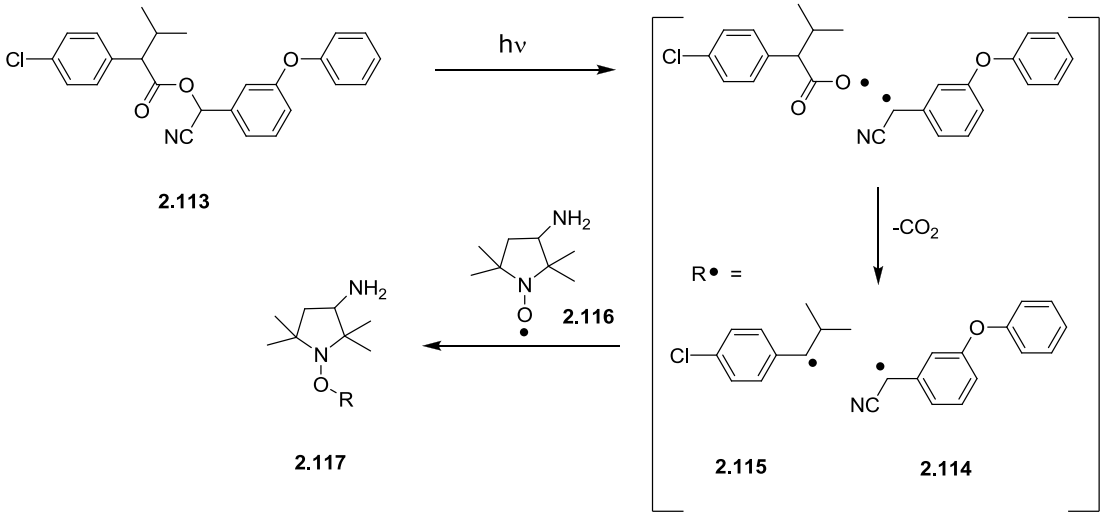
Azobisisobutyronitrile (AIBN) was employed to generate 2-cyanopropyl free radicals by photolysis or thermolysis as shown in **Scheme 2.23**. When the radical was trapped by the profluorescent naphthyl carboxylate nitroxide **2.1**, the fluorescence emission increased with a parallel decrease in the EPR signal. Alkoxylamine **2.112** was generated, which exhibited a 20-fold increase in fluorescence emission compared to the naphthalene nitroxide **2.1**.



Scheme 2.23 Generation of 2-cyanopropyl free radical followed by trapping with naphthalene nitroxide **2.1**

Other studies involving monitoring carbon-centered radicals by profluorescent nitroxides include the formation of benzylic radicals generated from the photolysis of dibenzyl ketone in an NaY zeolite,[63] photolysis of the pesticide fenvalerate,[100] and ketoenoxy radicals formed through enzymatic processes.[27] The eventual fate of pesticides in water is largely determined by photochemical reactions initiated by natural sunlight. Photodegradation of fenvalerate **2.113** is

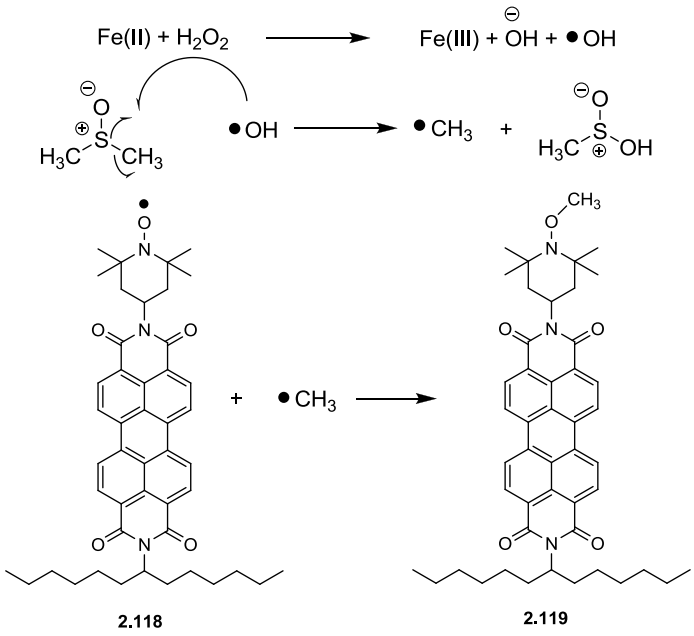
shown in **Scheme 2.24**. Upon irradiation, fenvalerate is cleaved to form phenoxybenzyl radical **2.114** and a transient radical that readily decarboxylates to from chlorobenzyl radical **2.115**. Suzuki and Katagi[100] demonstrated a method to trap the benzyl radicals **2.114** and **2.115** using pyrrolidinyl nitroxide **2.116**. The resulting alkoxylamine **2.117** was then coupled with fluorescamine **2.31** to generate a highly fluorescent adduct, as described before in **Scheme 2.6**.



Scheme 2.24 Phenoxybenzyl radical **2.114** and chlorobenzyl radical **2.115** were trapped by amino pyrrolidinyl nitroxide **2.116** to form alkoxyamines **2.117**.

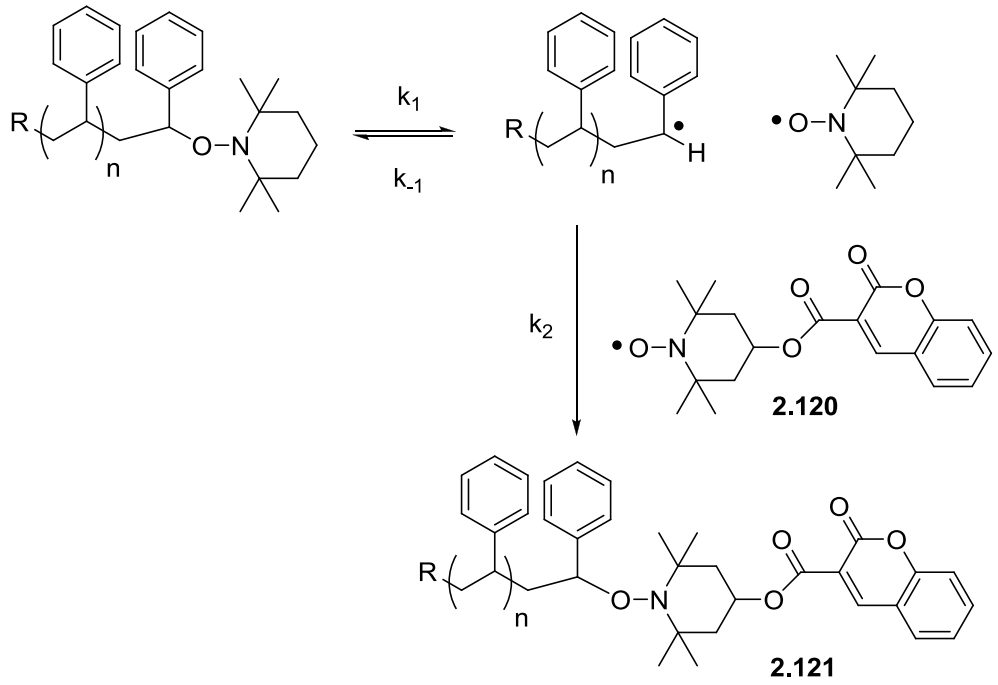
ROS can be detected indirectly by profluorescent nitroxides. Hydroxyl radical is one of the main reactive oxygen species implicated in DNA damage, lipid peroxidation, aging, cancer and other diseases.[101] Profluorescent nitroxide probes containing fluorophores such as naphthalene,[102, 103] anthracene[45] and fluorescamine[104-108] have been developed to detect hydroxyl radical. A novel

profluorescent nitroxide described as a "swallow-tailed perylene derivative for detecting hydroxyl radical" **2.118**, which has a longer wavelength for excitation and emission, was developed to avoid damage to living cells.[52] Nitroxide **2.118** was used to indirectly detect hydroxyl radical generated from the Fenton reaction as shown in **Scheme 2.25**. Fe(II) is oxidized by hydrogen peroxide to Fe(III), generating hydroxyl radical. Subsequent addition to DMSO expelled a methyl radical, which was then trapped by nitroxide **2.118** to form fluorescent alkoxylamine **2.119**. This system was selective for hydroxyl radical, since other ROS, including superoxide anion, nitric oxide, peroxynitrite, and alkyl peroxy radical, did not cause a significant increase in the fluorescence emission of profluorescent nitroxide **2.118**.



Scheme 2.25 Indirect monitoring of hydroxyl radical generated by Fenton chemistry, via trapping methyl radicals produced in the presence of DMSO

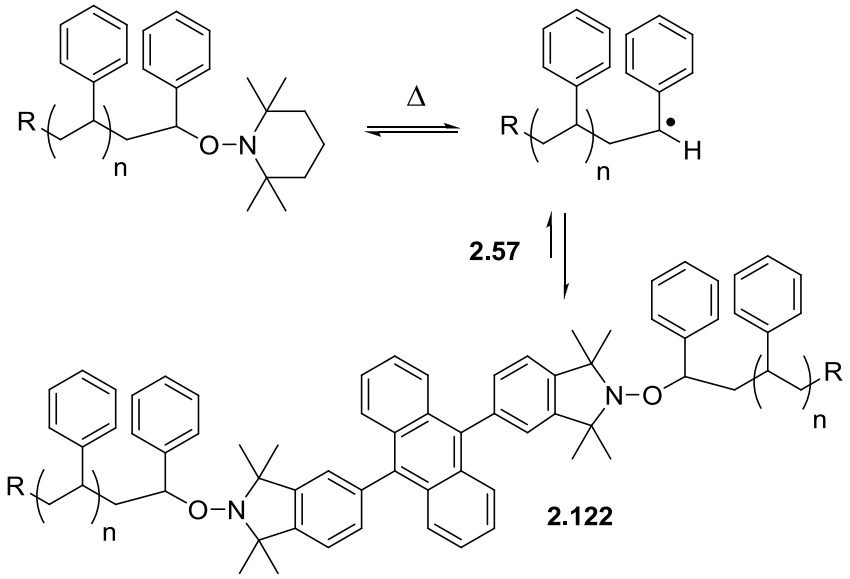
Profluorescent nitroxides are also useful in materials/polymer chemistry to monitor the formation of new functional polymers and also to follow degradation and aging of materials. In the field of controlled free radical polymerization, Scaiano and coworkers[109] exchanged the TEMPO cap with the profluorescent cap **2.120** (**Scheme 2.26**). Radical formation and bond dissociation rates were determined by monitoring the increase in fluorescence resulting from the formation of **2.121**.



Scheme 2.26 Scaiano's nitroxide cap exchange process

Bottle *et al*.[110, 111] extended this technique by employing the very stable profluorescent nitroxide **2.57** as the exchangable nitroxide cap, resulting in a stoichiometric and efficient exchange reaction. The fluorescent mid-chain

functionalized block copolymer **2.122** showed double the molecular weight was produced of the TEMPO terminated polymer, as shown in **Scheme 2.27**.



Scheme 2.27 Use of the nitroxide exchange reaction with a profluorescent bisnitroxide **2.57** to produce a fluorescently labeled block copolymer **2.122**

Profluorescent nitroxides have also utilized directly as mediating agents (initiators) in nitroxide mediated radical polymerization,[112, 113] and in low-temperature nitroxide-mediated photopolymerization.[114, 115] In material chemistry, the most common application of profluorescent nitroxides is the monitoring of the formation of radicals during polymer degradation.[46, 49, 50, 116-118] Scaiano *et al*.[25] demonstrated that carbon radical trapping could be observed within a solid polymer matrix by preparing thin poly(methyl methacrylate) (PMMA) films doped with profluorescent nitroxides **2.86** and **2.87** and radical photo-initiators. A mask was

applied and the film was exposed to light to photo-induce the formation of radicals, which were trapped by profluorescent nitroxides **2.86** and **2.87** to provide patterned polymer films, as shown in **Figure 2.13**. Later, Scaiano *et al*.[44] showed that thermally generated radicals could also be quantified by this technique. Profluorescent nitroxide **2.86** was used to trap isopropylnitrile radical formed upon the thermal decomposition of AIBN in PMMA thin film. By conducting temperature dependent studies, kinetic information such as the activation energy for the fragmentation of AIBN was determined.

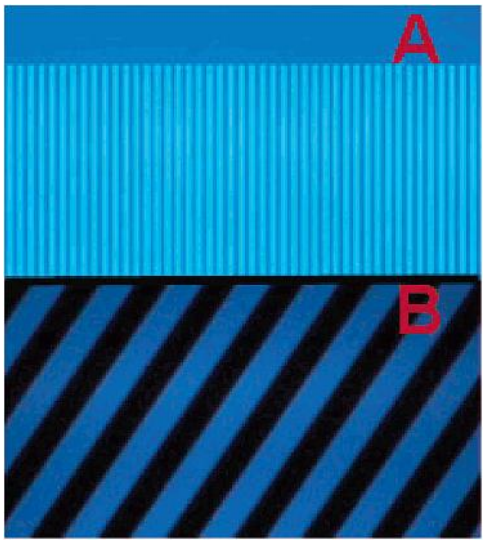


Figure 2.13 Fluorescent images (exposed regions emit light blue fluorescence) of PMMA film containing (**a**) nitroxide **2.86** and a photo-initiator obtained by exposure through a mask with 10-mm line spacing for 90s (**b**) nitroxide **2.87** and a photo-initiator obtained by exposure through a mask with 55-mm line spacing for 200s, adapted from Scaiano *et al*.[25]

Thermo-oxidative degradation of polypropylene film by exposing the film to oxygen at 150 °C for 10 hours (without an added free radical initiator) was investigated using a profluorescent isoindoline nitroxide.[24] The fluorescence increased as the polymer underwent autooxidation, generating radicals that were trapped by the nitroxide. Profluorescent nitroxides were recently utilized in environmental chemistry applications as detectors of ROS in particulate matter,[119] cigarette smoke,[120-124] combustion of biomasses,[125] and diesel exhaust.[120, 126, 127]

2.6 Nitroxide-Quantum Dot Sensors

2.6.2 Introduction to Quantum Dots

Semiconductor nanocrystals or "quantum dots" (QDs) are nanoscale crystalline particles usually surrounded by an outer layer of organic ligands to protect them against oxidation and aggregation. QDs are of particular interest because of their size-dependent photophysical, photochemical, and nonlinear optical properties.[128, 129] In contrast to the bulk materials, quantum dot particles exhibit quantum confinement effects that arise from their discrete energy levels as shown in **Figure 2.14**. The conduction band (antibonding orbitals) is the uppermost, almost unoccupied band encompassing a range of energies required to excite an electron from the valence band to move freely within the nanoparticle lattice. The valence band (bonding orbitals) is the lowermost, almost fully occupied

band analogous with the valence electrons of individual atoms. The energy difference between the valence band and the conduction band is known as the band gap (E_g).[130] When exposed to ultraviolet radiation, the energy released by QDs is inversely proportional to the size of the QD particles. In smaller nanoparticles, there

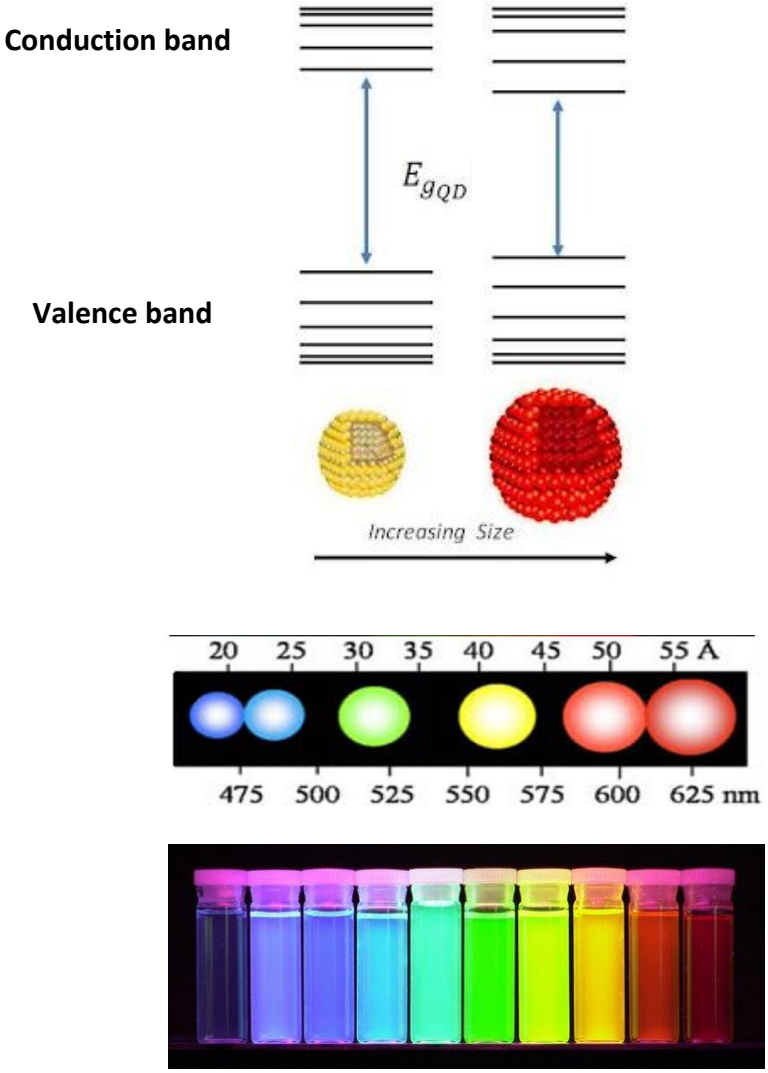


Figure 2.14 The energy diagram and the size-dependent fluorescence of quantum dots. Smaller QDs have larger band gaps comparing to large QDs: ranging from blue to red in color. Adapted from Klimov.[131]

are fewer energy levels, and electrons are held more tightly, resulting in a larger band gap and ultimately an emission that is higher in energy (lower wavelength, blue shift). As the size of the nanoparticle increases, the size of the band gap decreases, resulting in an emission that is red-shifted (lower energy, higher wavelength) as shown in **Figure 2.14**. As a consequence, QDs exhibit absorption and emission with energies characteristic of particle size, as shown in **Figure 2.15**.

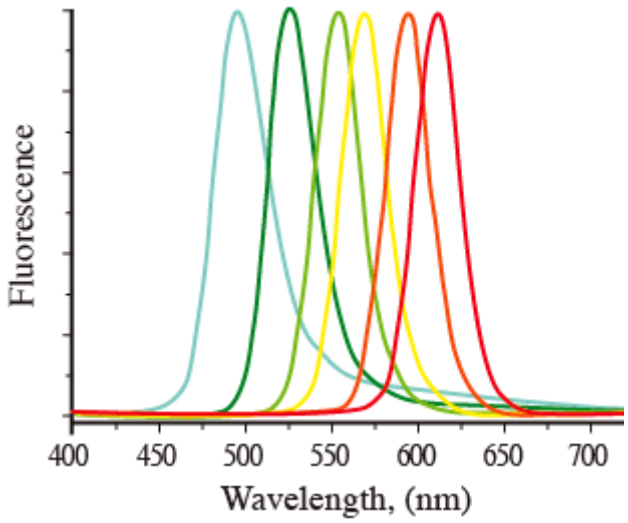


Figure 2.15 Emission spectra of increasing sizes of CdSe QDs from 2.0 to 5.5 nm: light blue to red color (excitation at 365 nm), adapted from http://www.aist.go.jp/aist_e/aist_today/2006_21/hot_line/hot_line_22.html

QDs have significant advantages over conventional organic fluorophores, such as their high quantum yield, excellent resistance to photobleaching, flexibility in excitation wavelength, narrow, symmetrical, and size-tunable emission spectra with a full width at half maximum (FWHM) of 20–30 nm, enabling the use of a single

excitation source for multicolor detection. They are often commercially available or accessibly by simple synthesis.[132, 133] QDs have been studied extensively for potential applications in laser optics,[134, 135] light emitting devices,[136-138] photovoltaic cells,[139-141] and molecular, cellular, and *in vivo* imaging.[142-147] QDs have the potential to overcome many of the limitations encountered by conventional organic fluorophores or genetically engineered fluorescent proteins for a variety of biological applications.[148-150] Comparisons of QDs to conventional organic fluorophores have been reported.[151, 152] Applications of nanoparticles in chemical and biosensors has been reviewed recently.[143, 153] The controlled quenching of fluorescent QDs has led to the development of probes in biology, medicine, and analytical chemistry as temperature,[154] protease-activation,[155] glutathione,[156] DNA,[157] spironolactone,[158] glucose,[159] copper ion,[160] anions,[161] nitric oxide,[162-164] hypochlorite,[165] formaldehyde,[166] and catecholamine[167] sensors.

2.6.2 Profluorescent Nitroxides with Quantum Dots as Fluorophores

Nitroxides not only quench the fluorescence emission of covalently linked organic dyes, but also diminish the strong fluorescence of quantum dots when they are in a close proximity. Scaiano *et al*. have investigated the quenching effect of the persistent nitroxide radical 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) on the emission of trioctylphosphine oxide (TOPO)-capped CdSe QDs in toluene solution.[168]

This quenching interaction followed the pattern that was previously reported by cyanide ions.[169] The quenching is nonlinear with respect to nitroxide concentration and strongly dependent on nanoparticle size: smaller particles are quenched more efficiently than larger particles as shown in **Figure 2.16**. Fluorescence spectra of 2.4 and 3.2 nm CdSe QDs in toluene were obtained with increasing concentrations of TEMPO. The fluorescence intensity at the shorter wavelength corresponding to the smaller particle decreases at a faster rate than the intensity at the longer wavelength. There was no specific binding between TEMPO and the QDs as confirmed by EPR spectroscopy. The N coupling constant, line width and amplitude remain unchanged upon addition of an equimolar amount of green QDs. This

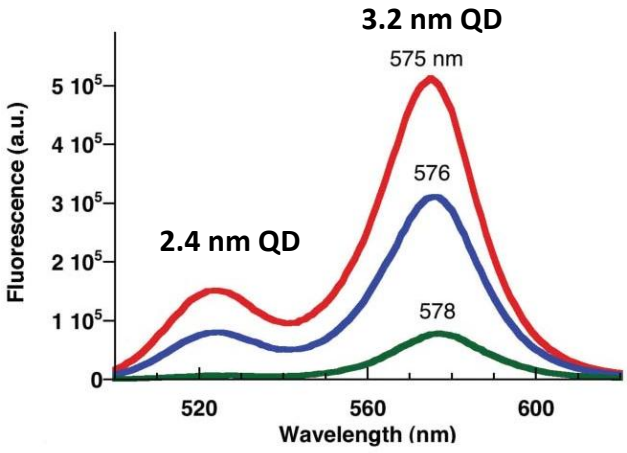


Figure 2.16 Fluorescence spectra (λ_{ex} 380 nm) of a toluene solution of 2.4 and 3.2 nm QD with the same concentrations (3.7 mM). Fluorescence intensity decreases as the concentration of TEMPO increases: 0 M (red), 0.04 M (blue), 0.2 M (green), as adapted from Scaiano *et al*.[168]

suggests dynamic fluorescence quenching predominates. The Stern-Volmer quenching plot shows an upward curvature (**Figure 2.17**). The values of dynamic quenching constants (α) obtained from the fits of Stern-Volmer plots to **Equation 2.2** are 1.6, 6.4 and 13.7 M^{-1} for large, medium and small dots, respectively. When

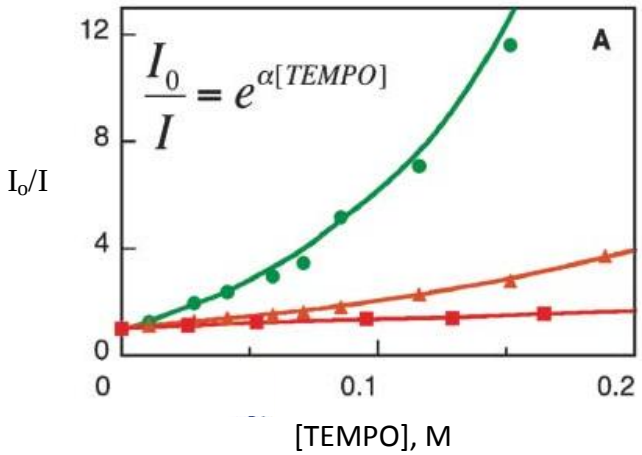


Figure 2.17 Fluorescent intensities of 2.4 (green), 3.2 (orange) and 6.7 (red) nm quantum dots with increasing concentrations of TEMPO, shown as a Stern–Volmer plot. I_o = the fluorescence maximum taken in the absence of TEMPO. I = fluorescence in the presence of TEMPO at each concentration. Adapted from Scaiano *et al*.[170]

$$\frac{I_0}{I} = e^{\alpha[\mathrm{TEMPO}]} \qquad \textbf{Equation 2.2}$$

the QD solution was saturated with TEMPO, there was an increasing chance for the collision between TEMPO and the QDs, resulting in a quenching of the QD fluorescence. The behavior in which fluorescence of smaller particles are quenched more efficiently than larger particles is described using the Perrin model[171] as shown

in **Figure 2.18**. The black dot represents the TEMPO quencher, and the grey shell represents the "sphere of action" that TEMPO has on the QDs. In the case of small particles (green 2.4 nm), TEMPO can reach across most of the nanoparticle area, while for the larger quantum dots (red 6.7 nm), the quencher can only interact with QDs near a limited region of the surface.[170] Scaiano proposed that the band gap and the curvature of the QDs contribute to the more effective quenching of the smaller QDs. The higher curvature provided a closer approach to the QD by the nitroxide quencher.

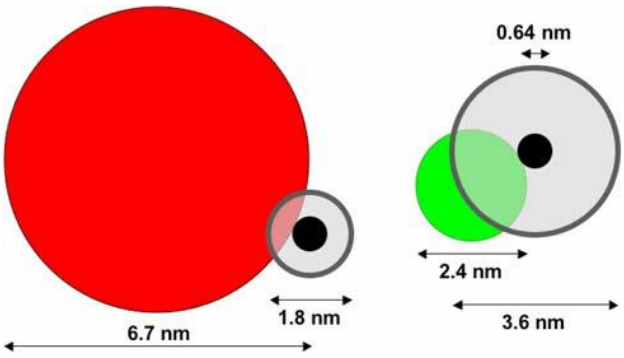


Figure 2.18 Schematic representation of "sphere of action" for the quencher, as adapted from Scaiano *et al*.[170] Black circle = TEMPO on the surface of QDs, red and green circles = red and green QDs, grey circle = sphere of action (Perrin radii)

Significantly, 4-amino-TEMPO is a much more efficient quencher, as compared to non-functionalized TEMPO, due to strong binding to the QD surface. The Stern-

Volmer plot for the ligand 4-amino-TEMPO is a downward curve (**Figure 2.19**), indicating that static quenching dominates. At high concentrations, as a number of

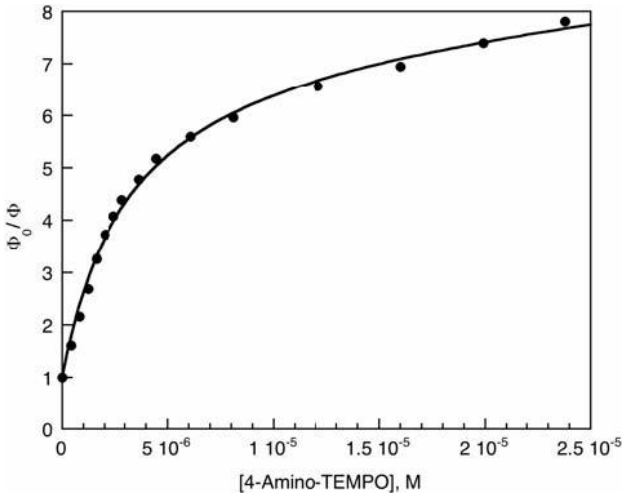
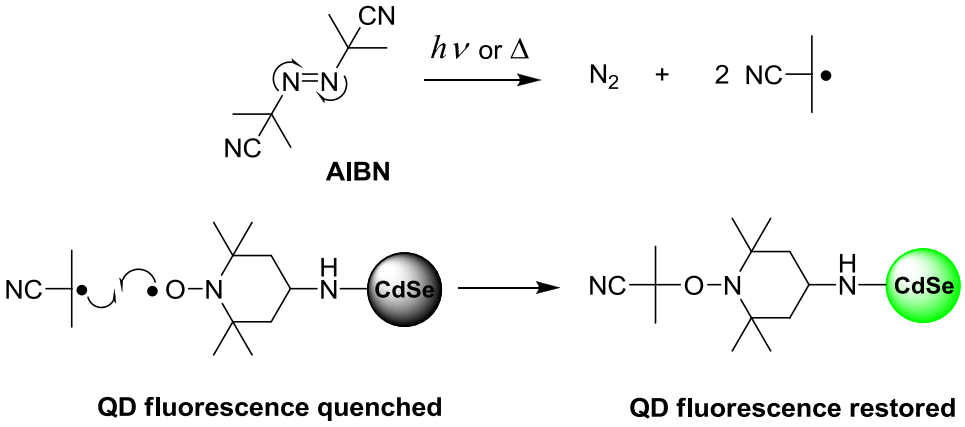


Figure 2.19 Quenching of fluorescence by 4-amino-TEMPO at the emission maximum for green QDs, shown as a Stern–Volmer plot, adapted from Scaiano *et al*.[172]

available empty sites for 4-amino TEMPO bind to the surface decreases, the quenching efficiency of 4-amino TEMPO decreases. Further quenching occurs by displacement of some of the TOPO ligands on the QD surface. The impact of binding of the amino group to the QD surface is significant. Quenching by 4-amino TEMPO is at least 3 orders of magnitude more efficient than by TEMPO. Fluorescence of the 4-amino-TEMPO-CdSe QD complex was restored by trapping the nitroxide with the carbon free radical isopropylnitrile, generated by the photoexcitation of azo-bis-isobutyronitrile (AIBN) as shown in **Scheme 2.28**.[172] 4-Amino TEMPO quenched 55% of the original CdSe fluorescence. During irradiation, the fluorescence increased over

time as shown in **Figure 2.20**. Eventually, the initially quenched QD fluorescence was completely recovered after 70s, and the recovered fluorescence was stable over longer irradiation times (180s), which demonstrates that the probe was not



Scheme 2.28 Fluorescence recovery was observed when 4-amino-TEMPO/CdSe QDs trapped the carbon radical generated by AIBN.

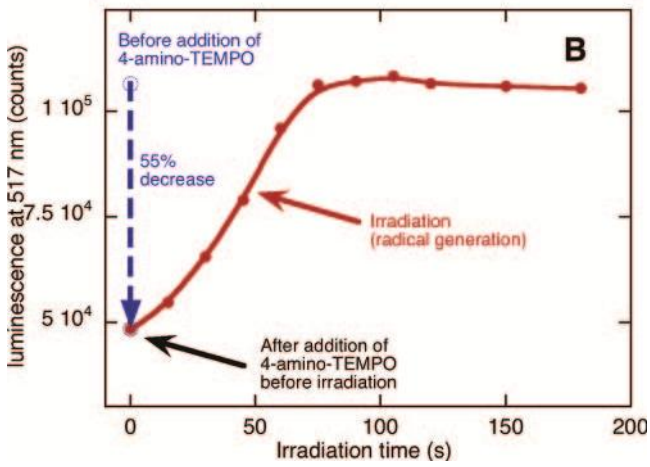


Figure 2.20 Fluorescence emission intensity at 517 nm of a toluene solution initially containing QDs and AIBN, followed by addition of 4-amino TEMPO and irradiation with UV-A ($\lambda > 340$ nm). Fluorescence was recovered to the initial level after 70s.

damaged by an excess of UV-A light or an excess of free radicals. EPR studies confirmed the absence of the nitroxide radicals. The quenching of core and core-shell CdSe quantum dots by TEMPO and 4-amino-TEMPO has been compared.[173] The efficiency of quenching is again strongly dependent on the nanoparticle size, the binding properties of the nitroxide, and the presence or absence of a ZnS protective shell on CdSe QDs. The shell only reduces the quenching efficiency significantly in the case of low concentrations of the binding 4-amino-TEMPO. This quenching is believed to be due to bound quenchers that attach to available surface sites: this is more efficient when the shell is not present. At higher nitroxide concentrations, fluorescence quenching efficiencies are not different between core and core/shell CdSe QDs. This is attributed to the displacement of TOPO from the surface by 4-amino TEMPO.

The CdSe surface was found to assist S-S bond cleavage of disulfide nitroxide diradical **2.123** introduced to the QD surface.[174] Disappearance of the biradical lines in the EPR spectra confirmed that the nitroxide moieties were no longer in proximity to one another once bonded to the QD surface, as shown in **Figure 2.21**. Addition of amines (cyclohexylamine, hexadecylamine) to QDs whose fluorescence had already been quenched by nitroxide **2.123** did not show any increase in emission intensity, in contrast to the case of 4-amino TEMPO, suggesting stronger binding by **2.123** than in

the case of amines. The catalytic activity of the CdSe surface on disulfide bond cleavage is now being investigated.

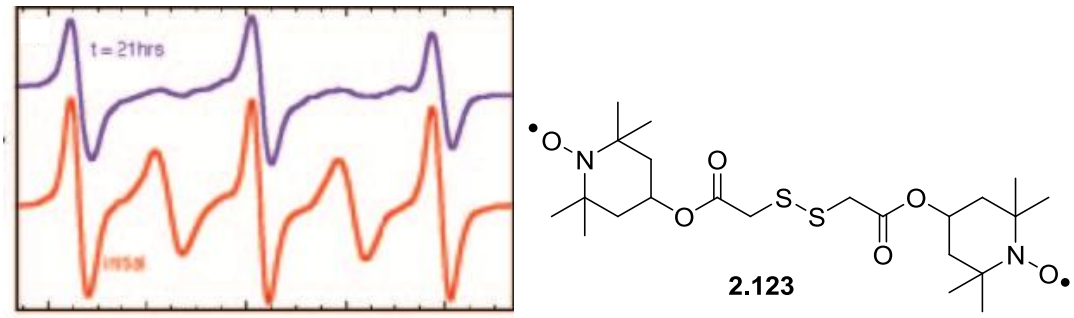
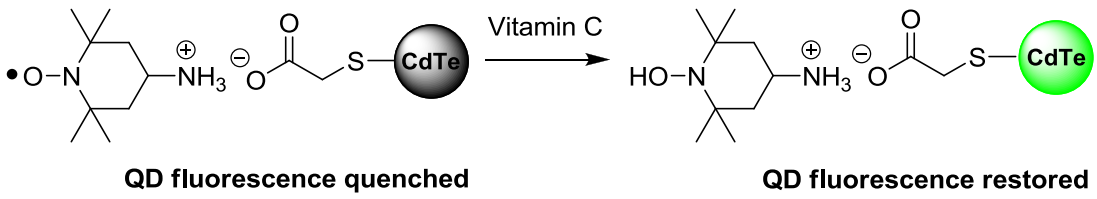


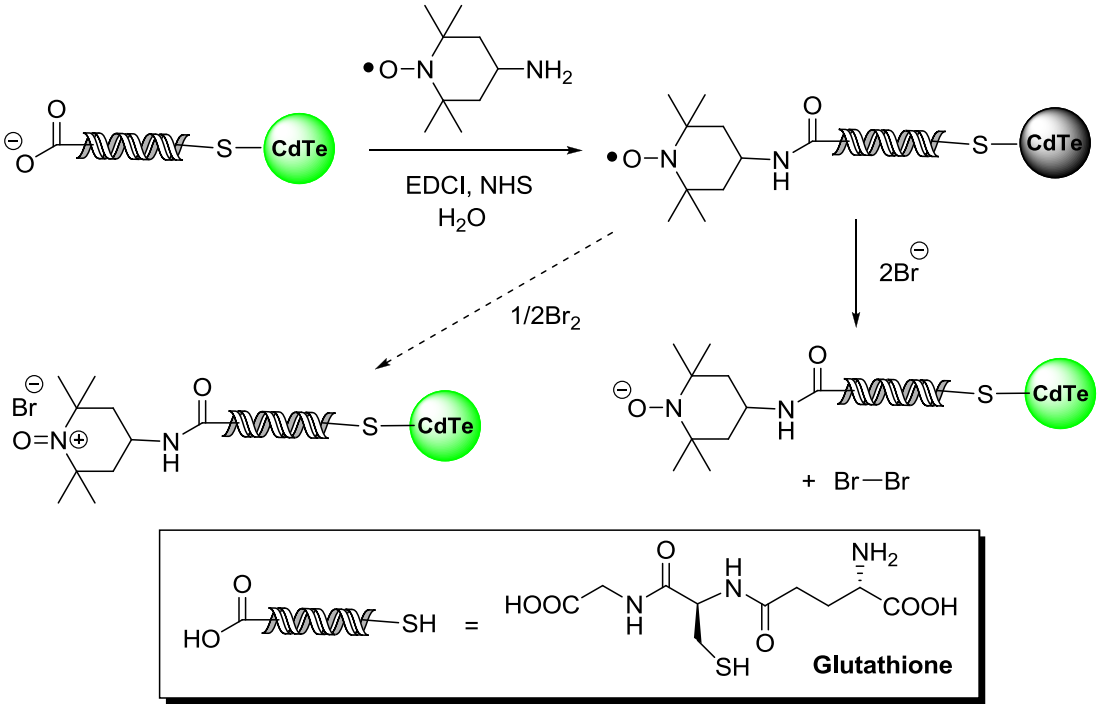
Figure 2.21 EPR spectra for nitroxide **2.123** in toluene after addition of CdSe QDs recorded immediately after mixing (red) and 21 h later (purple)

Guo and co-workers utilized water soluble thioglycolic acid-capped CdTe QDs conjugated to 4-amino-TEMPO as an acid/base salt to detect vitamin C by conversion of the paramagnetic nitroxide to the diamagnetic hydroxylamine, as shown in **Scheme 2.29**.[175] This system shows an upward curvature to the Stern-Volmer plot, even though 4-amino-TEMPO is held near the surface of the CdTe QDs by electrostatic interactions.



Scheme 2.29 Fluorescence quenching and recovery of CdTe QDs in aqueous media

Recently, 4-amino TEMPO was covalently linked with glutathione-capped CdTe QDs in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) (EDCI) and *N*-hydroxysuccinimide (NHS) for activation of the carboxylate group on glutathione (**Scheme 2.30**).[176] The fluorescence intensity of the 4-amino TEMPO-CdTe QDs nanoprobe was gradually enhanced in the presence of increasing concentrations of bromide ion. The authors assumed that the relative fluorescence enhancement in the presence of bromide ion is attributed to electron transfer from the bromide ion to 4-amino TEMPO to form *N*-hydroxyl anion. However, one-electron oxidation of nitroxides with dihalogen (Cl_2 or Br_2) provides oxoammonium cations with a halogen anion.[177-179] As a consequence, an alternative possibility is the oxidation of 4-amino TEMPO by bromine to form the oxoammonium salt as shown in **Scheme 2.30**, resulting in fluorescence recovery. The fluorescence intensity of the 4-amino TEMPO-CdTe QDs nanoprobe remained almost the same in the presence of K^+, Na^+, Mg^{2+}, Al^{3+}, I^-, CO_3^{2-}, Ac^-, Br^-, SO_3^{2-}, SO_4^{2-}, NO_3^-, Cl^- and F^-, even with concentrations 100 fold higher than that of the bromide ion (and thus bromine), indicating a high selectivity of the nanoprobe for the bromide ion over other ions. Distance-dependent fluorescence quenching and the binding of CdSe QDs by nitroxides with amine and carboxylic acid functionalities are discussed in Chapter 3.



Scheme 2.30 Coupling reaction of 4-amino TEMPO with glutathione-capped CdTe QDs resulted in fluorescence quenching. Reaction of bromide ion (or possibly bromine) with 4-amino TEMPO restored the QD fluorescence.

2.7 Conclusion

Profluorescent nitroxides have been utilized in diverse applications in the fields of biological, materials and environmental chemistry. A number of research groups have prepared profluorescent nitroxides using a variety of fluorophores, linkages and nitroxide structural designs. As fluorescent detection is extremely sensitive, the use of profluorescent nitroxides in the development of sensors is becoming increasingly popular. Redox changes and carbon-centered radicals can be effectively detected by an increase in fluorescence intensity, along with the

concurrent disappearance of nitroxide radical in EPR studies. A robust linkage between the nitroxide and the fluorophore is desired to prevent false positive responses, resulting from the chemical separation of the fluorophore and the nitroxide. Quantum dots are alternative inorganic fluorophores for applying profluorescent nitroxides in biological and material sciences, due to their highly intense fluorescence, good photostability, and flexibility in excitation wavelength.

2.8 References

1. Volodarski, L. B.; Reznikov, V. A.; Ovcharenko, V. I., *Synthetic Chemistry of Stable Nitroxides*. CRC Press, Inc.: Boca Raton, Florida, 1994.

2. Vogler, T.; Studer, A., *Synthesis-Stuttgart* **2008,** (13), 1979-1993.

3. Columbus, L.; Hubbell, W. L., *Trends in Biochemical Sciences* **2002,** *27* (6), 288-295.

4. Hustedt, E. J.; Beth, A. H., *Annual Review of Biophysics and Biomolecular Structure* **1999,** *28*, 129-153.

5. Janzen, E. G., *Accounts of Chemical Research* **1971,** *4* (1), 31-40.

6. Janzen, E. G.; Zhang, Y. K.; Haire, D. L., *Journal of the American Chemical Society* **1994,** *116* (9), 3738-3743.

7. Nakatsuji, S.; Anzai, H., *Journal of Materials Chemistry* **1997,** *7* (11), 2161-2174.

8. Caneschi, A.; Gatteschi, D.; Sessoli, R.; Rey, P., *Accounts of Chemical Research* **1989,** *22* (11), 392-398.

9. Qu, J.; Katsumata, T.; Satoh, M.; Wada, J.; Igarashi, J.; Mizoguchi, K.; Masuda, T., *Chemistry-A European Journal* **2007,** *13* (28), 7965-7973.

10. Buhrmester, C.; Moshurchak, L. M.; Wang, R. L.; Dahn, J. R., *Journal of the Electrochemical Society* **2006,** *153* (10), A1800-A1804.

11. Yonekuta, Y.; Susuki, K.; Oyaizu, K. C.; Honda, K. J.; Nishide, H., *Journal of the American Chemical Society* **2007,** *129* (46), 14128-14129.

12. Nesvadba, P., *Chimia* **2006,** *60* (12), 832-840.

13. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S., *Journal of Organic Chemistry* **1987,** *52* (12), 2559-2562.

14. Joseph, J.; Kalyanaraman, B.; Hyde, J. S., *Biochemical and Biophysical Research Communications* **1993,** *192* (2), 926-934.

15. Shen, J.; Bottle, S.; Khan, N.; Grinberg, O.; Reid, D.; Micallef, A.; Swartz, H., *Applied Magnetic Resonance* **2002,** *22* (3), 357-368.

16. Stryer, L.; Griffith, O. H., *Proceedings of the National Academy of Sciences of the United States of America* **1965,** *54* (6), 1785-1791.

17. Green, J. A.; Singer, L. A.; Parks, J. H., *Journal of Chemical Physics* **1973,** *58* (7), 2690-2695.

18. Green, J. A.; Singer, L. A., *Journal of the American Chemical Society* **1974,** *96* (9), 2730-2733.

19. Watkins, A. R., *Chemical Physics Letters* **1974,** *29* (4), 526-528.

20. Kuzmin, V. A.; Tatikolov, A. S., *Chemical Physics Letters* **1977,** *51* (1), 45-47.

21. Chattopadhyay, S. K.; Das, P. K.; Hug, G. L., *Journal of the American Chemical Society* **1983,** *105* (20), 6205-6210.

22. Scaiano, J. C.; Paraskevopoulos, C. I., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **1984,** *62* (11), 2351-2354.

23. Blough, N. V.; Simpson, D. J., *Journal of the American Chemical Society* **1988,** *110* (6), 1915-1917.

24. Micallef, A. S.; Blinco, J. P.; George, G. A.; Reid, D. A.; Rizzardo, E.; Thang, S. H.; Bottle, S. E., *Polymer Degradation and Stability* **2005,** *89* (3), 427-435.

25. Coenjarts, C.; Garcia, O.; Llauger, L.; Palfreyman, J.; Vinette, A. L.; Scaiano, J. C., *Journal of the American Chemical Society* **2003,** *125* (3), 620-621.

26. Dang, Y. M.; Guo, X. Q., *Applied Spectroscopy* **2006,** *60* (2), 203-207.

27. Ivan, M. G.; Scaiano, J. C., *Photochemistry and Photobiology* **2003,** *78* (4), 416-419.

28. Hideg, K.; Kalai, T.; Sar, C. P., *Journal of Heterocyclic Chemistry* **2005,** *42* (3), 437-450.

29. Medvedeva, N.; Martin, V. V.; Weis, A. L.; Likhtenshten, G. I., *Journal of Photochemistry and Photobiology A-Chemistry* **2004,** *163* (1-2), 45-51.

30. Blinco, J. P.; Fairfull-Smith, K. E.; Morrow, B. J.; Bottle, S. E., *Australian Journal of Chemistry* **2011,** *64* (4), 373-389.

31. Abrams, F. S.; London, E., *Biochemistry* **1993,** *32* (40), 10826-10831.

32. Asuncionpunzalan, E.; London, E., *Biochemistry* **1995,** *34* (36), 11460-11466.

33. Kaiser, R. D.; London, E., *Biochemistry* **1998,** *37* (22), 8180-8190.

34. Kachel, K.; Asuncionpunzalan, E.; London, E., *Biochemistry* **1995,** *34* (47), 15475-15479.

35. Weiss, D. S., *Journal of Photochemistry* **1977,** *6* (4), 301-304.

36. Green, S. A.; Simpson, D. J.; Zhou, G.; Ho, P. S.; Blough, N. V., *Journal of the American Chemical Society* **1990,** *112* (20), 7337-7346.

37. Gijzeman, O. L.; Kaufman, F.; Porter, G., *Journal of the Chemical Society-Faraday Transactions I* **1973,** *69* (5), 727-737.

38. Likhtenstein, G. I.; Ishii, K.; Nakatsuji, S., *Photochemistry and Photobiology* **2007,** *83* (4), 871-881.

39. Matko, J.; Ohki, K.; Edidin, M., *Biochemistry* **1992,** *31* (3), 703-711.

40. Sato, S.; Suzuki, M.; Soma, T.; Tsunoda, M., *Spectrochimica Acta Part A-Molecular and Biomolecular Spectroscopy* **2008,** *70* (4), 799-804.

41. Bognar, B.; Osz, E.; Hideg, K.; Kalai, T., *Journal of Heterocyclic Chemistry* **2006,** *43* (1), 81-86.

42. Bueno, C.; Mikelsons, L.; Maretti, L.; Scaiano, J. C.; Aspée, A., *Photochemistry and Photobiology* **2008,** *84* (6), 1535-1542.

43. Besson, T.; Coudert, G.; Guillaumet, G., *Journal of Heterocyclic Chemistry* **1991,** *28* (6), 1517-1523.

44. Aspée, A.; Garcia, O.; Maretti, L.; Sastre, R.; Scaiano, J. C., *Macromolecules* **2003,** *36* (10), 3550-3556.

45. Yang, X. F.; Guo, X. Q., *Analyst* **2001,** *126* (10), 1800-1804.

46. Danko, M.; Chmela, T.; Hrdlovič, P., *Polymer Degradation and Stability* **2003,** *79* (2), 333-343.

47. Likhtenshtein, G. I., *Pure and Applied Chemistry* **2008,** *80* (10), 2125-2139.

48. Jockusch, S.; Dedola, G.; Lem, G.; Turro, N. J., *Journal of Physical Chemistry B* **1999,** *103* (43), 9126-9129.

49. Kollar, J.; Hrdlovič, P.; Chmela, S., *Journal of Photochemistry and Photobiology A-Chemistry* **2009,** *204* (2-3), 191-199.

50. Hrdlovič, P.; Chmela, S.; Danko, M., *Journal of Photochemistry and Photobiology A-Chemistry* **1998,** *112* (2-3), 197-203.

51. Hrdlovič, P.; Chmela, S.; Danko, M.; Sarakha, M.; Guyot, G., *Journal of Fluorescence* **2008,** *18* (2), 393-402.

52. Maki, T.; Soh, N.; Fukaminato, T.; Nakajima, H.; Nakano, K.; Imato, T., *Analytica Chimica Acta* **2009,** *639* (1-2), 78-82.

53. Kollar, J.; Hrdlovič, P.; Chmela, S.; Sarakha, M.; Guyot, G., *Journal of Photochemistry and Photobiology A-Chemistry* **2005,** *170* (2), 151-159.

54. Lozinsky, E.; Martin, V. V.; Berezina, T. A.; Shames, A. I.; Weis, A. L.; Likhtenshtein, G. I., *Journal of Biochemical and Biophysical Methods* **1999,** *38* (1), 29-42.

55. Kalai, T.; Hideg, E.; Vass, I.; Hideg, K., *Free Radical Biology and Medicine* **1998,** *24* (4), 649-652.

56. Hideg, E.; Kalai, T.; Kos, P. B.; Asada, K.; Hideg, K., *Photochemistry and Photobiology* **2006,** *82* (5), 1211-1218.

57. Ziessel, R.; Stroh, C., *Synthesis-Stuttgart* **2003,** (14), 2145-2154.

58. Ziessel, R.; Stroh, C., *Organic Letters* **2003,** *5* (14), 2397-2400.

59. Herbelin, S. E.; Blough, N. V., *Journal of Physical Chemistry B* **1998,** *102* (42), 8170-8176.

60. Johnson, C. G.; Caron, S.; Blough, N. V., *Analytical Chemistry* **1996,** *68* (5), 867-872.

61. Kieber, D. J.; Blough, N. V., *Analytical Chemistry* **1990,** *62* (21), 2275-2283.

62. Vaughan, P. P.; Blough, N. V., *Environmental Science & Technology* **1998,** *32* (19), 2947-2953.

63. Aspée, A.; Maretti, L.; Scaiano, J. C., *Photochemical & Photobiological Sciences* **2003,** *2* (11), 1125-1129.

64. Lozinsky, E. M.; Martina, L. V.; Shames, A. I.; Uzlaner, N.; Masarwa, A.; Likhtenshtein, G. I.; Meyerstein, D.; Martin, V. V.; Priel, Z., *Analytical Biochemistry* **2004,** *326* (2), 139-145.

65. Keddie, D. J.; Johnson, T. E.; Arnold, D. P.; Bottle, S. E., *Organic & Biomolecular Chemistry* **2005,** *3* (14), 2593-2598.

66. Fairfull-Smith, K. E.; Bottle, S. E., *European Journal of Organic Chemistry* **2008,** (32), 5391-5400.

67. Keddie, D. J.; Fairfull-Smith, K. E.; Bottle, S. E., *Organic & Biomolecular Chemistry* **2008,** *6* (17), 3135-3143.

68. Blinco, J. P.; McMurtrie, J. C.; Bottle, S. E., *European Journal of Organic Chemistry* **2007,** (28), 4638-4641.

69. Kalai, T.; Balog, M.; Jeko, J.; Hubbell, W. L.; Hideg, K., *Synthesis-Stuttgart* **2002,** (16), 2365-2372.

70. Kalai, T.; Jeko, J.; Berente, Z.; Hideg, K., *Synthesis-Stuttgart* **2006,** (3), 439-446.

71. Stroh, C.; Mayor, M.; von Hanisch, C., *European Journal of Organic Chemistry* **2005,** (17), 3697-3703.

72. Morrow, B. J.; Keddie, D. J.; Gueven, N.; Lavin, M. F.; Bottle, S. E., *Free Radical Biology and Medicine* **2010,** *49* (1), 67-76.

73. Hosokawa, K.; Chen, P.; Lavin, M. F.; Bottle, S. E., *Free Radical Biology and Medicine* **2004,** *37* (7), 946-952.

74. Fairfull-Smith, K. E.; Brackmann, F.; Bottle, S. E., *European Journal of Organic Chemistry* **2009,** (12), 1902-1915.

75. Ahn, H.-Y.; Fairfull-Smith, K. E.; Morrow, B. J.; Lussini, V.; Kim, B.; Bondar, M. V.; Bottle, S. E.; Belfield, K. D., *Journal of the American Chemical Society* **2012,** *134* (10), 4721-4730.

76. Wang, H. M.; Zhang, D. Q.; Guo, X. F.; Zhu, L. Y.; Shuai, Z. G.; Zhu, D. B., *Chemical Communications* **2004,** (6), 670-671.

77. Li, J.; Wang, H. M.; Ma, H. M.; Zhang, D. Q.; Xiong, S. X., *Chinese Chemical Letters* **2005,** *16* (8), 1125-1128.

78. Bognar, B.; Jeko, J.; Kalai, T.; Hideg, K., *Dyes and Pigments* **2010,** *87* (3), 218-224.

79. Morris, J. C.; McMurtrie, J. C.; Bottle, S. E.; Fairfull-Smith, K. E., *Journal of Organic Chemistry* **2011,** *76* (12), 4964-4972.

80. Lozinsky, E.; Novoselsky, A.; Shames, A. I.; Saphier, O.; Likhtenshtein, G. I.; Meyerstein, D., *Biochimica Et Biophysica Acta-General Subjects* **2001,** *1526* (1), 53-60.

81. Saphier, O.; Silberstein, T.; Shames, A. I.; Likhtenshtein, G. I.; Maimon, E.; Mankuta, D.; Mazor, M.; Katz, M.; Meyerstein, D.; Meyerstein, N., *Free Radical Research* **2003,** *37* (3), 301-308.

82. Aspée, A.; Orrego, A.; Alarcón, E.; López-Alarcón, C.; Poblete, H.; Gónzalez-Nilo, D., *Bioorganic & Medicinal Chemistry Letters* **2009,** *19* (22), 6382-6385.

83. Sato, S.; Tsunoda, M.; Suzuki, M.; Kutsuna, M.; Takido-Uchi, K.; Shindo, M.; Mizuguchi, H.; Obara, H.; Ohya, H., *Spectrochimica Acta Part A-Molecular and Biomolecular Spectroscopy* **2009,** *71* (5), 2030-2039.

84. Barhate, N.; Cekan, P.; Massey, A. P.; Sigurdsson, S. T., *Angewandte Chemie-International Edition* **2007,** *46* (15), 2655-2658.

85. Cekan, P.; Smith, A. L.; Barhate, N.; Robinson, B. H.; Sigurdsson, S. T., *Nucleic Acids Research* **2008,** *36* (18), 5946-5954.

86. Batz, M.; Korth, H. G.; Sustmann, R., *Angewandte Chemie-International Edition in English* **1997,** *36* (13-14), 1501-1503.

87. Meineke, P.; Rauen, U.; de Groot, H.; Korth, H. G.; Sustmann, R., *Chemistry-A European Journal* **1999,** *5* (6), 1738-1747.

88. Duppe, P. M.; Talbierski, P. M.; Hornig, F. S.; Rauen, U.; Korth, H. G.; Wille, T.; Boese, R.; Omlor, T.; de Groot, H.; Sustmann, R., *Chemistry-A European Journal* **2010,** *16* (36), 11121-11132.

89. Tang, Y. L.; He, F.; Yu, M. H.; Wang, S.; Li, Y. L.; Zhu, D. B., *Chemistry of Materials* **2006,** *18* (16), 3605-3610.

90. Veerman, E. C. I.; Nazmi, K.; van Hof, W.; Bolscher, J. G. M.; den Hertog, A. L.; Amerongen, A. V. N., *Biochemical Journal* **2004,** *381*, 447-452.

91. Borisenko, G. G.; Martin, I.; Zhao, Q.; Amoscato, A. A.; Tyurina, Y. Y.; Kagan, V. E., *Journal of Biological Chemistry* **2004,** *279* (22), 23453-23462.

92. Borisenko, G. G.; Martin, I.; Zhao, Q.; Amoscato, A.; Kagan, V. E., *Journal of the American Chemical Society* **2004,** *126* (30), 9221-9232.

93. Aspée, A.; Allaga, C.; Scaiano, J. C., *Photochemistry and Photobiology* **2007,** *83* (3), 481-485.

94. Aliaga, C.; Juárez-Ruiz, J. M.; Scaiano, J. C.; Aspée, A., *Organic Letters* **2008,** *10* (11), 2147-2150.

95. Aliaga, C.; Aspée, A.; Scaiano, J. C., *Organic Letters* **2003,** *5* (22), 4145-4148.

96. Jia, M.; Tang, Y.; Lam, Y. F.; Green, S. A.; Blough, N. V., *Analytical Chemistry* **2009,** *81* (19), 8033-8040.

97. Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U., *Journal of the American Chemical Society* **1992,** *114* (13), 4983-4992.

98. Gerlock, J. L.; Zacmanidis, P. J.; Bauer, D. R.; Simpson, D. J.; Blough, N. V.; Salmeen, I. T., *Free Radical Research Communications* **1990,** *10* (1-2), 119-121.

99. Kieber, D. J.; Blough, N. V., *Free Radical Research Communications* **1990,** *10* (1-2), 109-117.

100. Suzuki, Y.; Katagi, T., *Journal of Agricultural and Food Chemistry* **2008,** *56* (22), 10811-10816.

101. Tatla, S.; Woodhead, V.; Foreman, J. C.; Chain, B. M., *Free Radical Biology and Medicine* **1999,** *26* (1-2), 14-24.

102. Yang, X. F.; Guo, X. Q., *Analytica Chimica Acta* **2001,** *434* (2), 169-177.

103. Bian, Z. Y.; Guo, X. Q.; Zhao, Y. B.; Du, J. O., *Analytical Sciences* **2005,** *21* (5), 553-559.

104. Li, B. B.; Gutierrez, P. L.; Amstad, P.; Blough, N. V., *Chemical Research in Toxicology* **1999,** *12* (11), 1042-1049.

105. Li, B. B.; Blough, N. V.; Gutierrez, P. L., *Free Radical Biology and Medicine* **2000,** *29* (6), 548-556.

106. Thomas-Smith, T. E.; Blough, N. V., *Environmental Science & Technology* **2001,** *35* (13), 2721-2726.

107. Pou, S.; Huang, Y. I.; Bhan, A.; Bhadti, V. S.; Hosmane, R. S.; Wu, S. Y.; Cao, G. L.; Rosen, G. M., *Analytical Biochemistry* **1993,** *212* (1), 85-90.

108. Li, B. B.; Gutierrez, P. L.; Blough, N. V., *Analytical Chemistry* **1997,** *69* (21), 4295-4302.

109. Ballesteros, O. G.; Maretti, L.; Sastre, R.; Scaiano, J. C., *Macromolecules* **2001,** *34* (18), 6184-6187.

110. Fairfull-Smith, K. E.; Blinco, J. P.; Keddie, D. J.; George, G. A.; Bottle, S. E., *Macromolecules* **2008,** *41* (5), 1577-1580.

111. Blinco, J. P.; Fairfull-Smith, K. E.; Micaller, A. S.; Bottle, S. E., *Polymer Chemistry* **2010,** *1* (7), 1009-1012.

112. Goto, A.; Scaiano, J. C.; Maretti, L., *Photochemical & Photobiological Sciences* **2007,** *6* (8), 833-835.

113. Colwell, J. M.; Blinco, J. P.; Hulbert, C.; Fairfull-Smith, K. E.; Bottle, S. E., *Australian Journal of Chemistry* **2011,** *64* (4), 426-432.

114. Guillaneuf, Y.; Bertin, D.; Gigmes, D.; Versace, D. L.; Lalevee, J.; Fouassier, J. P., *Macromolecules* **2010,** *43* (5), 2204-2212.

115. Versace, D. L.; Lalevee, J.; Fouassier, J. P.; Guillaneuf, Y.; Bertin, D.; Gigmes, D., *Macromolecular Rapid Communications* **2010,** *31* (15), 1383-1388.

116. Blinco, J. P.; Keddie, D. J.; Wade, T.; Barker, P. J.; George, G. A.; Bottle, S. E., *Polymer Degradation and Stability* **2008,** *93* (9), 1613-1618.

117. Colwell, J. M.; Walker, J. R.; Blinco, J. P.; Micallef, A. S.; George, G. A.; Bottle, S. E., *Polymer Degradation and Stability* **2010,** *95* (10), 2101-2109.

118. Moghaddam, L.; Blinco, J. P.; Colwell, J. M.; Halley, P. J.; Bottle, S. E.; Fredericks, P. M.; George, G. A., *Polymer Degradation and Stability* **2011,** *96* (4), 455-461.

119. Alaghmand, M.; Blough, N. V., *Environmental Science & Technology* **2007,** *41* (7), 2364-2370.

120. Flicker, T. M.; Green, S. A., *Analytical Chemistry* **1998,** *70* (9), 2008-2012.

121. Flicker, T. M.; Green, S. A., *Environmental Health Perspectives* **2001,** *109* (8), 765-771.

122. Bartalis, J.; Chan, W. G.; Wooten, J. B., *Analytical Chemistry* **2007,** *79* (13), 5103-5106.

123. Bartalis, J.; Zhao, Y. L.; Flora, J. W.; Paine, J. B.; Wooten, J. B., *Analytical Chemistry* **2009,** *81* (2), 631-641.

124. Miljevic, B.; Fairfull-Smith, K. E.; Bottle, S. E.; Ristovski, Z. D., *Atmospheric Environment* **2010,** *44* (18), 2224-2230.

125. Miljevic, B.; Heringa, M. F.; Keller, A.; Meyer, N. K.; Good, J.; Lauber, A.; Decarlo, P. F.; Fairfull-Smith, K. E.; Nussbaumer, T.; Burtscher, H.; Prevot, A. S. H.; Baltensperger, U.; Bottle, S. E.; Ristovski, Z. D., *Environmental Science & Technology* **2010,** *44* (17), 6601-6607.

126. Surawski, N. C.; Miljevic, B.; Roberts, B. A.; Modini, R. L.; Situ, R.; Brown, R. J.; Bottle, S. E.; Ristovski, Z. D., *Environmental Science & Technology* **2010,** *44* (1), 229-235.

127. Surawski, N. C.; Miljevic, B.; Ayoko, G. A.; Roberts, B. A.; Elbagir, S.; Fairfull-Smith, K. E.; Bottle, S. E.; Ristovski, Z. D., *Environmental Science & Technology* **2011,** *45* (13), 5498-5505.

128. Alivisatos, A. P., *Science* **1996,** *271* (5251), 933-937.

129. Rossetti, R.; Hull, R.; Gibson, J. M.; Brus, L. E., *Journal of Chemical Physics* **1985,** *82* (1), 552-559.

130. Martin, R., *Electronic Structure: Basic Theory and Practical Methods*. Cambridge University Press: UK, 2004.

131. Klimov, V., *Los Alamos Science* **2003,** *28*, 214-220.

132. Smith, A. M.; Gao, X. H.; Nie, S. M., *Photochemistry and Photobiology* **2004,** *80* (3), 377-385.

133. Gao, X. H.; Yang, L. L.; Petros, J. A.; Marshal, F. F.; Simons, J. W.; Nie, S. M., *Current Opinion in Biotechnology* **2005,** *16* (1), 63-72.

134. Wuister, S. F.; Swart, I.; van Driel, F.; Hickey, S. G.; Donega, C. D., *Nano Letters* **2003,** *3* (4), 503-507.

135. Klimov, V. I.; Mikhailovsky, A. A.; Xu, S.; Malko, A.; Hollingsworth, J. A.; Leatherdale, C. A.; Eisler, H. J.; Bawendi, M. G., *Science* **2000,** *290* (5490), 314-317.

136. Colvin, V. L.; Schlamp, M. C.; Alivisatos, A. P., *Nature* **1994,** *370* (6488), 354-357.

137. Coe, S.; Woo, W. K.; Bawendi, M.; Bulovic, V., *Nature* **2002,** *420* (6917), 800-803.

138. Lee, J.; Sundar, V. C.; Heine, J. R.; Bawendi, M. G.; Jensen, K. F., *Advanced Materials* **2000,** *12* (15), 1102-1105.

139. Johnston, K. W.; Pattantyus-Abraham, A. G.; Clifford, J. P.; Myrskog, S. H.; MacNeil, D. D.; Levina, L.; Sargent, E. H., *Applied Physics Letters* **2008,** *92* (15).

140. Greenham, N. C.; Peng, X. G.; Alivisatos, A. P., *Physical Review B* **1996,** *54* (24), 17628-17637.

141. Huynh, W. U.; Dittmer, J. J.; Alivisatos, A. P., *Science* **2002,** *295* (5564), 2425-2427.

142. Lidke, D. S.; Nagy, P.; Heintzmann, R.; Arndt-Jovin, D. J.; Post, J. N.; Grecco, H. E.; Jares-Erijman, E. A.; Jovin, T. M., *Nature Biotechnology* **2004,** *22* (2), 198-203.

143. Somers, R. C.; Bawendi, M. G.; Nocera, D. G., *Chemical Society Reviews* **2007,** *36* (4), 579-591.

144. Zimmer, J. P.; Kim, S. W.; Ohnishi, S.; Tanaka, E.; Frangioni, J. V.; Bawendi, M. G., *Journal of the American Chemical Society* **2006,** *128* (8), 2526-2527.

145. Kim, S.; Lim, Y. T.; Soltesz, E. G.; De Grand, A. M.; Lee, J.; Nakayama, A.; Parker, J. A.; Mihaljevic, T.; Laurence, R. G.; Dor, D. M.; Cohn, L. H.; Bawendi, M. G.; Frangioni, J. V., *Nature Biotechnology* **2004,** *22* (1), 93-97.

146. Medintz, I. L.; Uyeda, H. T.; Goldman, E. R.; Mattoussi, H., *Nature Materials* **2005,** *4* (6), 435-446.

147. Gill, R.; Zayats, M.; Willner, I., *Angewandte Chemie-International Edition* **2008,** *47* (40), 7602-7625.

148. Feng, C.-L.; Zhong, X.; Steinhart, M.; Caminade, A.-M.; Majoral, J.-P.; Knoll, W., *Advanced Materials* **2007,** *19* (15), 1933-1936.

149. Jaiswal, J. K.; Mattoussi, H.; Mauro, J. M.; Simon, S. M., *Nature Biotechnology* **2003,** *21* (1), 47-51.

150. Gao, X. H.; Cui, Y. Y.; Levenson, R. M.; Chung, L. W. K.; Nie, S. M., *Nature Biotechnology* **2004,** *22* (8), 969-976.

151. Schroeder, T., *Nature* **2008,** *453* (7193), 345-351.

152. Resch-Genger, U.; Grabolle, M.; Cavaliere-Jaricot, S.; Nitschke, R.; Nann, T., *Nature Methods* **2008,** *5* (9), 763-775.

153. Raymo, F. M.; Yildiz, I., *Physical Chemistry Chemical Physics* **2007,** *9* (17), 2036-2043.

154. Walker, G. W.; Sundar, V. C.; Rudzinski, C. M.; Wun, A. W.; Bawendi, M. G.; Nocera, D. G., *Applied Physics Letters* **2003,** *83* (17), 3555-3557.

155. Chang, E.; Miller, J. S.; Sun, J. T.; Yu, W. W.; Colvin, V. L.; Drezek, R.; West, J. L., *Biochemical and Biophysical Research Communications* **2005,** *334* (4), 1317-1321.

156. Banerjee, S.; Kar, S.; Perez, J. M.; Santra, S., *Journal of Physical Chemistry C* **2009,** *113* (22), 9659-9663.

157. Dyadyusha, L.; Yin, H.; Jaiswal, S.; Brown, T.; Baumberg, J. J.; Booy, F. P.; Melvin, T., *Chemical Communications* **2005,** (25), 3201-3203.

158. Liang, J. G.; Huang, S.; Zeng, D. Y.; He, Z. K.; Ji, X. H.; Ai, X. P.; Yang, H. X., *Talanta* **2006,** *69* (1), 126-130.

159. Cordes, D. B.; Gamsey, S.; Singaram, B., *Angewandte Chemie-International Edition* **2006,** *45* (23), 3829-3832.

160. Jin, T.; Fujii, F.; Yamada, E.; Nodasaka, Y.; Kinjo, M., *Combinatorial Chemistry & High Throughput Screening* **2007,** *10* (6), 473-479.

161. Callan, J. F.; Mulrooney, R. C.; Kamila, S.; McCaughan, B., *Journal of Fluorescence* **2008,** *18* (2), 527-532.

162. Fabregat, V.; Angeles Izquierdo, M.; Isabel Burguete, M.; Galindo, F.; Luis, S. V., *Inorganica Chimica Acta* **2012,** *381*, 212-217.

163. Wadhavane, P. D.; Angeles Izquierdo, M.; Galindo, F.; Isabel Burguete, M.; Luis, S. V., *Soft Matter* **2012,** *8* (16), 4373-4381.

164. Neuman, D.; Ostrowski, A. D.; Mikhailovsky, A. A.; Absalonson, R. O.; Strouse, G. F.; Ford, P. C., *Journal of the American Chemical Society* **2008,** *130* (1), 168-175.

165. Yan, Y.; Wang, S.; Liu, Z.; Wang, H.; Huang, D., *Analytical Chemistry* **2010,** *82* (23), 9775-9781.

166. Ma, Q.; Cui, H.; Su, X., *Biosensors & Bioelectronics* **2009,** *25* (4), 839-844.

167. Ma, Y.; Yang, C.; Li, N.; Yang, X. R., *Talanta* **2005,** *67* (5), 979-983.

168. Laferriere, M.; Galian, R. E.; Maurel, V.; Scaiano, J. C., *Chemical Communications* **2006,** (3), 257-259.

169. Jin, W. J.; Fernandez-Arguelles, M. T.; Costa-Fernandez, J. M.; Pereiro, R.; Sanz-Medel, A., *Chemical Communications* **2005,** (7), 883-885.

170. Scaiano, J. C.; Laferriere, M.; Galian, R. E.; Maurel, V.; Billone, P., *Physica Status Solidi a-Applications and Materials Science* **2006,** *203* (6), 1337-1343.

171. Turro, N. J., Modern Molecular Photochemistry. Benjamin Cummings Publishing Co.: Menlo Park, 1978; p 628.

172. Maurel, V.; Laferriere, M.; Billone, P.; Godin, R.; Scaiano, J. C., *Journal of Physical Chemistry B* **2006,** *110* (33), 16353-16358.

173. Heafey, E.; Laferriere, M.; Scaiano, J. C., *Photochemical & Photobiological Sciences* **2007,** *6* (5), 580-584.

174. Billone, P. S.; Maretti, L.; Maurel, V.; Scaiano, J. C., *Journal of the American Chemical Society* **2007,** *129* (46), 14150-14151.

175. Chen, W. B.; Wang, X.; Tu, X. J.; Pei, D. J.; Zhao, Y.; Guo, X. Q., *Small* **2008,** *4* (6), 759-764.

176. Adegoke, O.; Hosten, E.; McCleland, C.; Nyokong, T., *Analytica Chimica Acta* **2012,** *721*, 154-161.

177. Liu, W.; Howarth, M.; Greytak, A. B.; Zheng, Y.; Nocera, D. G.; Ting, A. Y.; Bawendi, M. G., *Journal of the American Chemical Society* **2008,** *130* (4), 1274-1284.

178. Bobbitt, J. M.; Flores, M. C. L., *Heterocycles* **1988,** *27* (2), 509-533.

179. Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M., *Journal of Organic Chemistry* **1985,** *50* (8), 1332-1334.

Chapter 3: Distance-dependent Fluorescence Quenching and Binding of CdSe Quantum Dots by Functionalized Nitroxide Radicals

3.1 Introduction

Semiconductor nanoparticles or quantum dots (QDs) have received much attention because of their tunable luminescent properties, making them attractive for various sensing[1, 2] and imaging[3-7] applications. The controlled quenching of QD fluorescence has given rise to the development of numerous functional sensors (see Chapter 2). This chapter describes the synthesis of nitroxides bearing functionalities that bind strongly to highly fluorescent CdSe QDs. Upon binding, these ligated nitroxides quench the QD fluorescence. Fluorescence is restored when the surface-bound nitroxides are reduced to hydroxylamines or trapped with a carbon radical. Fluorescence and electron paramagnetic resonance (EPR) studies were performed to examine the fluorescence quenching efficiency of nitroxides bound to the surface of a CdSe QD as a function of proximity of the nitroxide to the ligand, and thus to the QD surface, and variation of the ligand binding affinities. These results provide new fundamental insights into the process of fluorescence quenching of QDs by nitroxides as well as electron transfer or spin exchange between QDs and nitroxide radicals. This work has been published: C. Tansakul, E. Lilie, E. D. Walter, F. Rivera III,

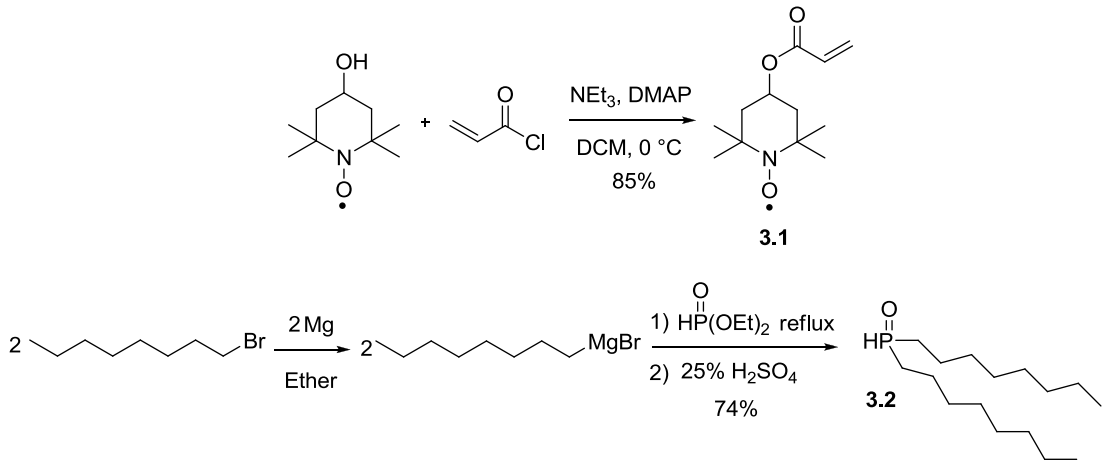
A. Wolcott, J. Z. Zhang, G. L. Millhauser, R. Braslau *J. Phys. Chem. C,* **2010**, *114,* 7793-7805. A portion of this chapter's discussion is adapted directly from this publication.

3.2 Synthesis of Functionalized Nitroxides

3.2.1 Attempted Synthesis of Nitroxides bearing a Phosphine Oxide or Phosphanate Ligand

A typical synthesis of high quality CdSe nanoparticles gives the core semiconductor stabilized by aliphatic phosphines, phosphine oxides, and/or phosphonic acids bound on the nanoparticle surface. In order to mimic the structure of the common phosphine oxide ligand on QD surfaces, and simultaneously provide nitroxide as a fluorescence quenching moiety, it was desired to tether dioctylphosphine oxide (DOPO) to 4-hydroxy-2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPOL). Two starting materials were synthesized, as shown in **Scheme 3.1**. 4-Acryloyloxy-2,2,6,6-tetramethylpiperidin-*N*-oxyl **3.1** was synthesized via acyl substitution using TEMPOL adding to acryloyl chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) in dichloromethane (DCM).[8] Column chromatography afforded nitroxide **3.1** in 85% yield. A solution of octylmagnesium bromide was prepared from *n*-bromooctane and magnesium metal in diethyl ether. Diethylphosphite was then refluxed with freshly prepared

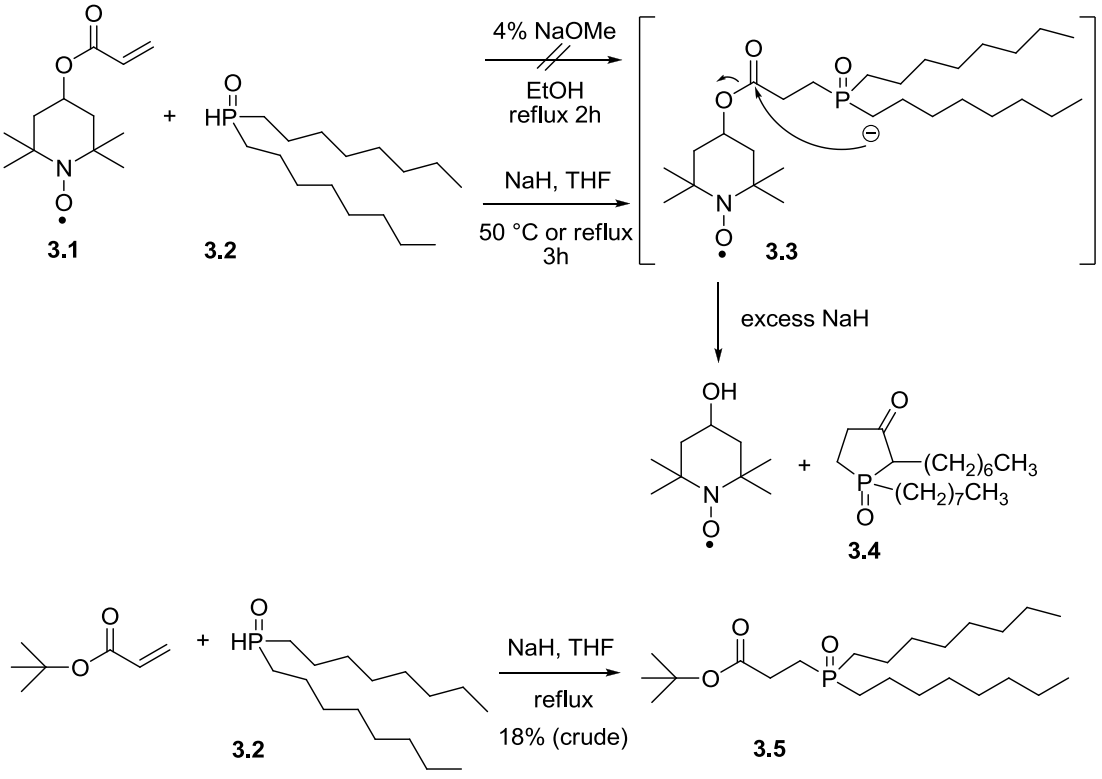
octylmagnesium bromide to give DOPO **3.2** in 74% yield after precipitation with 25% sulfuric acid.[9]



Scheme 3.1 Synthesis of nitroxide **3.1** and DOPO **3.2**

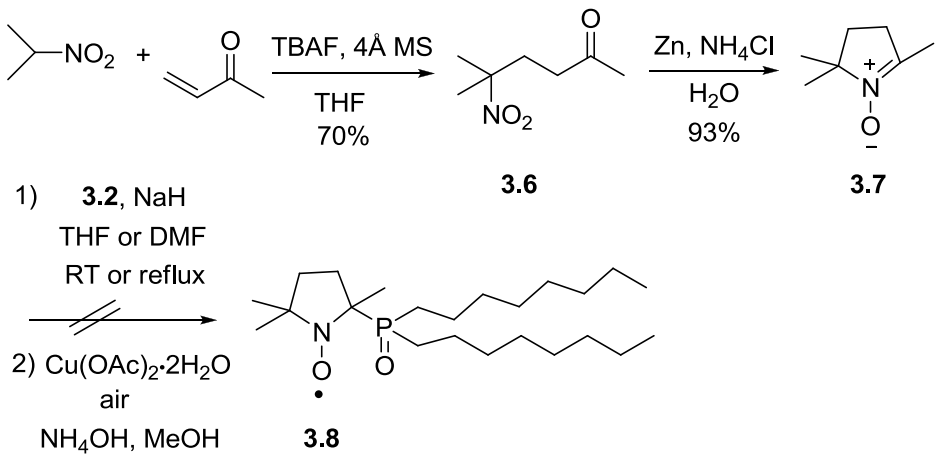
With nitroxide **3.1** and DOPO **3.2** in hand, synthesis of nitroxide **3.3** was attempted as shown in **Scheme 3.2**. In an initial attempt, both of the starting materials were refluxed in the presence of 4% sodium methoxide as a base.[10] The second attempt used sodium hydride as a base in tetrahydrofuran (THF) at 50 °C.[11] The final attempt involved heating the reaction mixture at reflux with sodium hydride. However, none of the desired product was formed. In the cases employing sodium hydride, excess base apparently deprotonated the methylene position next to the phosphorus atom. The anion then attacked the ester carbonyl, resulting in the degradation of the expected product into a cyclic phosphine oxide **3.4** and TEMPOL, which was observed by ^{1}H NMR: δ 4.01 (m, 1H), 1.90 (doublet of multiplet, 2H), 1.54

(t, *J* = 12 Hz, 2H), 1.25 (s, 6H), 1.18 (s, 6H) ppm in $CDCl_3$. A model reaction was carried out using *tert*-butyl acrylate, to give *tert*-butyl-3-(dioctylphosphinoyl) propanoate **3.5** in only 18% crude yield, as shown in **Scheme 3.2**. Without purification, the identity of the crude product was confirmed by ^{1}H NMR: δ 2.56-2.52 (m, 2H), 2.42-1.18 (m, 28H), 1.98-1.89 (m, 2H), 1.45 (9H), 0.92-8.84 (m, 6H) ppm in $CDCl_3$, and low resolution mass spectrometry (LRMS): $[M+H]^+$ = 403.5. Thus it appears that the product is unstable to base.



Scheme 3.2 Attempted synthesis of nitroxide bearing phosphine oxide **3.3**, and a model reaction

Synthesis of nitroxide **3.8** bearing the phosphine oxide close to the nitroxide functionality was attempted as shown in **Scheme 3.3**. The plan involved addition of the anion of DOPO **3.2** to nitrone **3.7**, followed by oxidation to give nitroxide **3.8**.

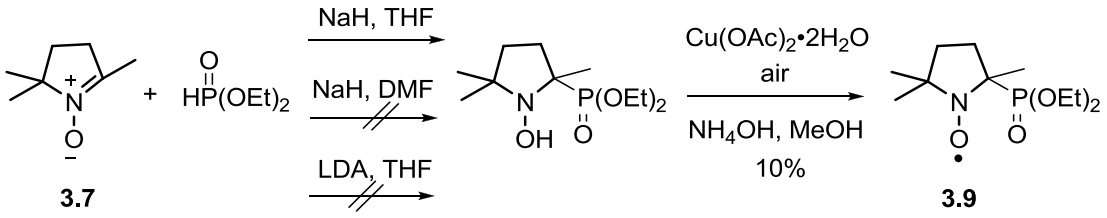


Scheme 3.3 Attempted synthesis of nitroxide **3.8** bearing phosphine oxide ligand

To make nitrone **3.7**, 5-methyl-5-nitrohexan-2-one **3.6** was synthesized via the Michael addition of the anion of 2-methyl-2-nitropropane to methyl vinyl ketone in the presence of tetrabutylammonium fluoride (TBAF) as the base, and activated 4 Å molecular sieves in THF.[12] The nitro compound **3.6** was obtained in 70% yield after column chromatography. Reductive cyclization of **3.6** using ammonium chloride and zinc metal provided 3,4-dihydro-2,2,5-trimethyl-2*H*-pyrrole-1-oxide **3.7**[13] in 93% yield. Several attempts to achieve the addition of DOPO to nitrone **3.7** were carried out. First nitrone **3.7** was refluxed with DOPO **3.2** in the presence of sodium hydride

in THF. Catalytic cupric acetate and air were then used with the intention of oxidizing the hydroxyamine to nitroxide, but no desired product was formed. The second attempt was similar, but was carried out at room temperature. The final attempt involved reaction at room temperature in dimethylformamide (DMF). However, again no product was formed.

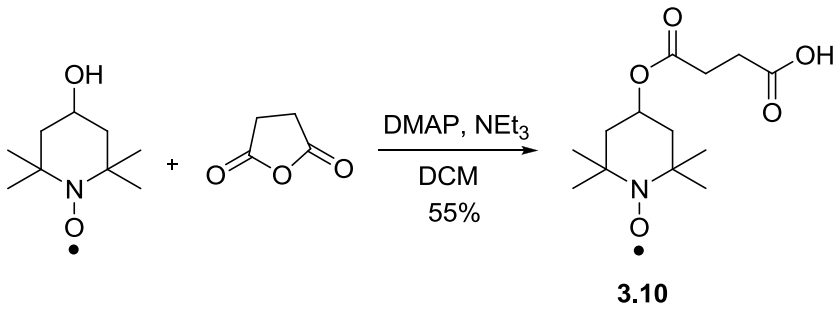
Nitroxide **3.9** bearing the phosphonate functional group was synthesized as shown in **Scheme 3.4**. The nitrone **3.7** was combined with diethylphosphite in the presence of sodium hydride in THF. Catalytic cupric acetate and air were used to oxidize the hydroxyamine to give 2,5,5-trimethyl-2-diethylphosphite-pyrrolidin-*N*-oxyl **3.9** in only 10% yield. Switching the solvent from THF to DMF did not result in the desired product. It was assumed that the nucleophile attacked the carbonyl group of DMF instead of adding to the nitrone. The next attempt used lithium diisopropylamide (LDA) as a base; however there was no product formed.



Scheme 3.4 Synthesis of nitroxide **3.9** bearing phosphanate ligand

3.2.2 Synthesis of a Nitroxide bearing a Carboxylic Acid Ligand

A recent mechanistic study[14] argues that a phosphonic acid, not a phosphine oxide, is the functional ligand on the surface of cadmium or zinc chalcogenides. As a consequence, attention was turned to the use of a carboxylic acid instead of an alkyl phosphine oxide as a ligand for QDs. Nitroxide **3.10** was synthesized by the opening of succinic anhydride using TEMPOL in the presence of triethylamine as shown in **Scheme 3.5**. Column chromatography afforded 4-(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yloxy)-4-oxobutanoic acid **3.10** in 55% yield.[15]

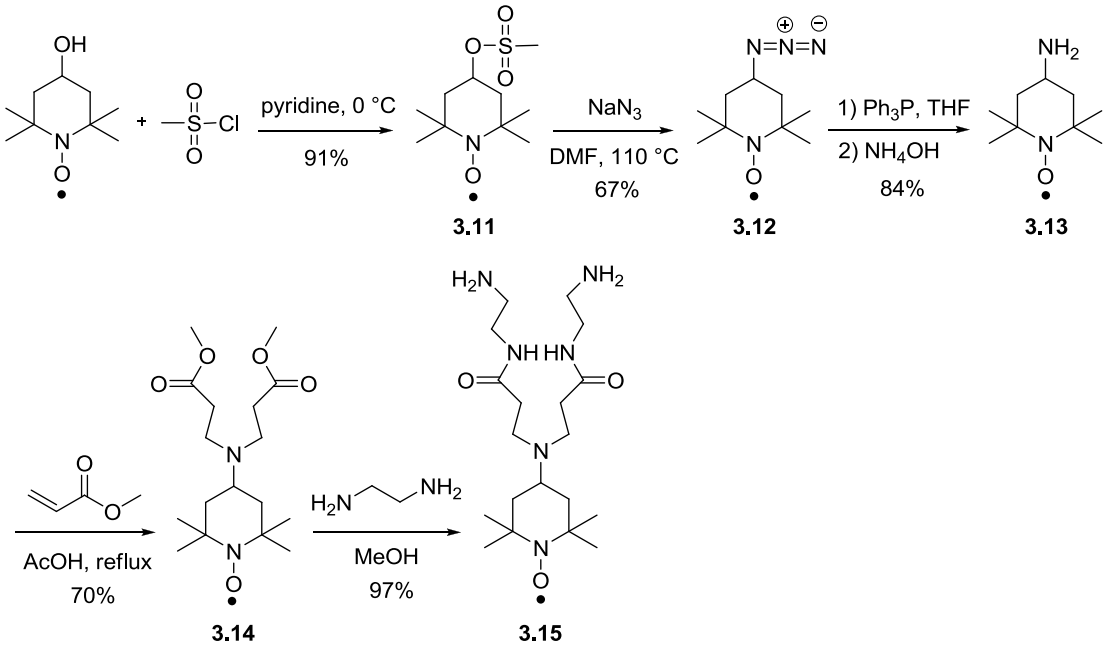


3.10

Scheme 3.5 Synthesis of nitroxide **3.10** bearing carboxylic acid ligand

3.2.3 Synthesis of Nitroxides bearing an Amine or Bisamine Ligand

The amine functionality is an effective ligand for the surface of CdSe QDs. 4-Amino TEMPO **3.13**, and a novel bidentate amine bearing TEMPO **3.15**, inspired by the synthesis of polyamideamino (PAMAM) dendrimers,[16] were synthesized as shown in **Scheme 3.6**. The methanesulfonyl leaving group was introduced onto

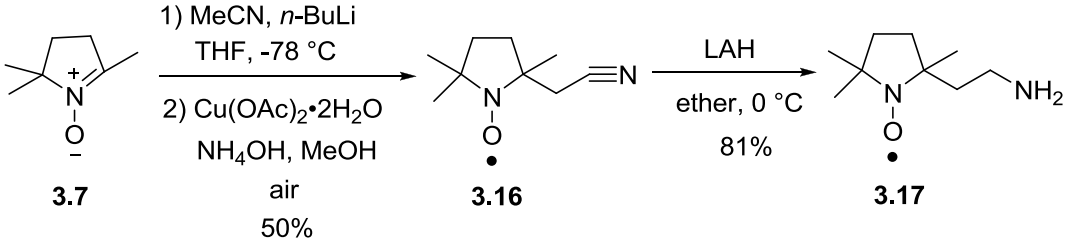


Scheme 3.6 Synthesis of 4-amino TEMPO **3.13** and bisamino nitroxide **3.15**

TEMPOL by addition of methanesulfonyl chloride in pyridine to give 4-methanesulfonyl-2,2,6,6-tetramethylpiperidin-*N*-oxyl **3.11** in 91% yield. The methanesulfonyl group was displaced with azide in DMF at 110 °C to give 4-azido-2,2,6,6-tetramethylpiperidin-*N*-oxyl **3.12** in 67% yield. Staudinger reduction using triphenylphosphine and ammonium hydroxide afforded 4-amino-2,2,6,6-tetramethylpiperidin-*N*-oxyl (4-amino TEMPO) **3.13** in 84% yield.[17] 4-Amino TEMPO **3.13** was refluxed with methyl acrylate in the presence of glacial acetic acid[18] to give 3,3′-(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl-amino)-*N*,*N*-bispropionic acid dimethyl ester **3.14** in 70% yield after column chromatography. The reaction of **3.14** with

ethylenediamine in methanol[18] gave 97% yield of the desired bidentate amine 3,3′-(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl-azanediyl)bis(*N*-(2-aminoethyl)propana mide) **3.15**.

In an effort to decrease the distance between the nitroxide and the quantum dot, and thus increase the quenching efficiency, a nitroxide with a pendant amine group close to the nitroxide functionality was synthesized. The known amino pyrrolidine nitroxide **3.17** was synthesized by graduate student Frank Rivera III, as shown in **Scheme 3.7**. Deprotonation of acetonitrile (MeCN) with *n*-butyl lithium, followed by nucleophilic addition to the nitrone **3.7**, and subsequent oxidation with catalytic cupric acetate and air afforded 2-cyanomethyl-2,5,5-trimethylpyrrolidin-*N*-oxyl **3.16**[19] in 50% yield. Reduction of the nitrile with lithium aluminum hydride (LAH) provided the desired amine nitroxide 2-(2-aminoethyl)-2,5,5-trimethylpyrrolidin-*N*-oxyl **3.17**[19] in 81% yield.



Scheme 3.7 Synthesis of amino pyrrolidine nitroxide **3.17** by Frank Rivera III

The parent nitroxide 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO), and four nitroxides bearing carboxylic acid (carboxylic acid **3.10**) or amine ligands (amino pyrrolidine **3.17**, 4-amino TEMPO **3.13**, bisamino **3.15**), **Figure 3.1**, were investigated with CdSe QDs by EPR and fluorescence spectroscopy.

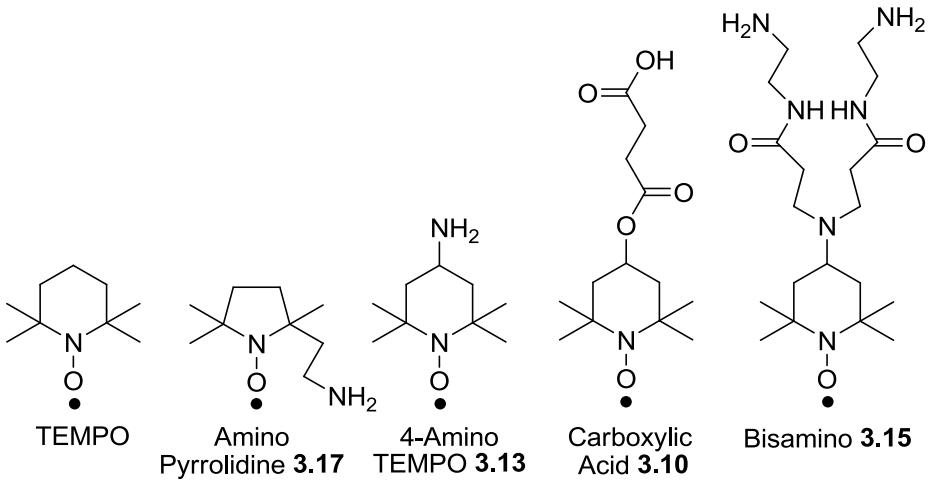


Figure 3.1 Nitroxides utilized in EPR and fluorescence studies

3.3 Electron Magnetic Resonance (EPR) Studies

3.3.1 Binding Affinities

The characteristic EPR spectra of TEMPO-based nitroxides exhibit three ^{14}N hyperfine lines separated by a splitting of 1.546 mT in toluene or benzene solutions.[20] EPR investigations on the interaction between the non-functionalized nitroxide TEMPO and CdSe QDs by Scaiano *et al*.[21] (see Chapter 2) suggest that no specific binding occurs between TEMPO and the QDs: the *N* coupling constant, line width, and amplitude of the TEMPO signal remains unchanged upon addition of

QDs. However, addition of QDs to a solution of 4-amino-TEMPO **3.13** leads to extensive broadening of the EPR signal and to a lower relative intensity of the high

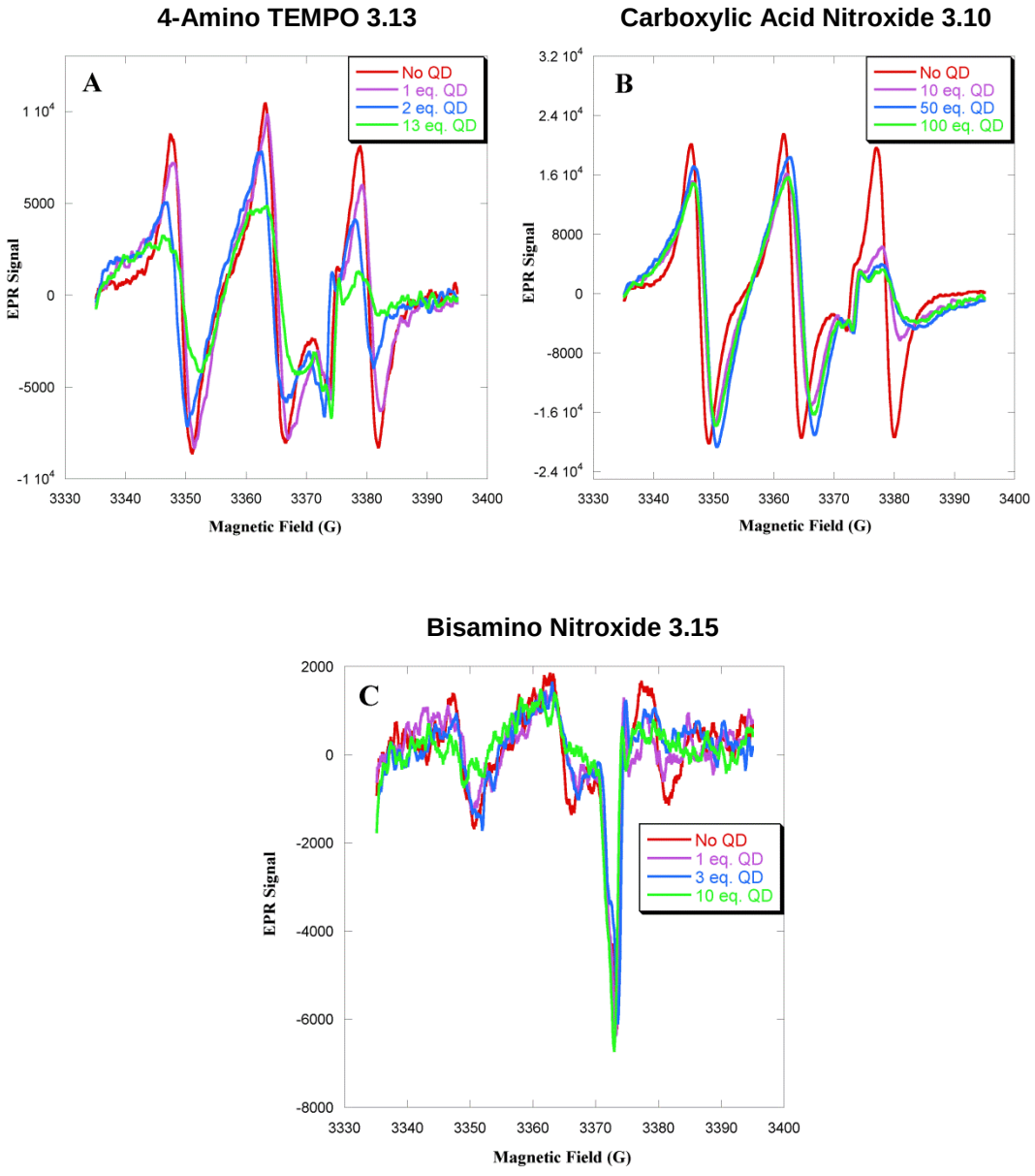


Figure 3.2A-C EPR spectra of nitroxides **3.13**, **3.10** and **3.15** (1 μM) in toluene upon successive addition of a solution of 3.7 nm CdSe QDs (note: eq. = equivalent)

field signal.[22] EPR spectra of the ligand-bearing nitroxides 4-amino TEMPO **3.13** (**Figure 3.2A**), carboxylic acid nitroxide **3.10** (**Figure 3.2B**), and bisamine nitroxide **3.15** (**Figure 3.2C**) in toluene show the expected characteristic ^{14}N hyperfine splitting; however the peaks are very broad, and the signal intensity is very low, especially for bisamino nitroxide **3.15**. Moreover, addition of CdSe QDs did not cause a significant change in the EPR signal. Since the triplet state of molecular oxygen is diradical, dissolved oxygen in toluene solution interrupts the EPR signals of these nitroxides. As a result, deaerated solvents are necessary to avoid line broadening caused by dissolved oxygen, thus allowing the accurate determination of binding constants. Determination of the QD concentration is described in Chapter 6.

EPR spectra of ligand-bearing nitroxides in **Figure 3.1** in deaerated toluene exhibit the expected sharp strong signals, as illustrated in **Figure 3.3A-D** (red lines). Successive addition of orange 3.7 nm diameter CdSe QDs to a solution of 4-amino-TEMPO **3.13** or carboxylic acid nitroxide **3.10** led to broadening of the EPR signals, accompanied by a reduction in peak-to-peak height, particularly at the high field peak. For example, upon addition of 10 equivalents of CdSe QDs to carboxylic acid nitroxide **3.10** (**Figure 3.3C**, black line), the two peaks at low and central fields are strongly broadened, and the peak-to-peak height at the high-field peak is much smaller than those at central and low fields. This broadening is indicative of restricted mobility and slow tumbling of the nitroxide as a result of binding to the

QD surface.[23] This type of behavior in the EPR spectrum has been previously observed with nitroxides bound to gold nanoparticles,[24] incorporated into DNA stands,[25] and immersed in lipid membranes.[26, 27]

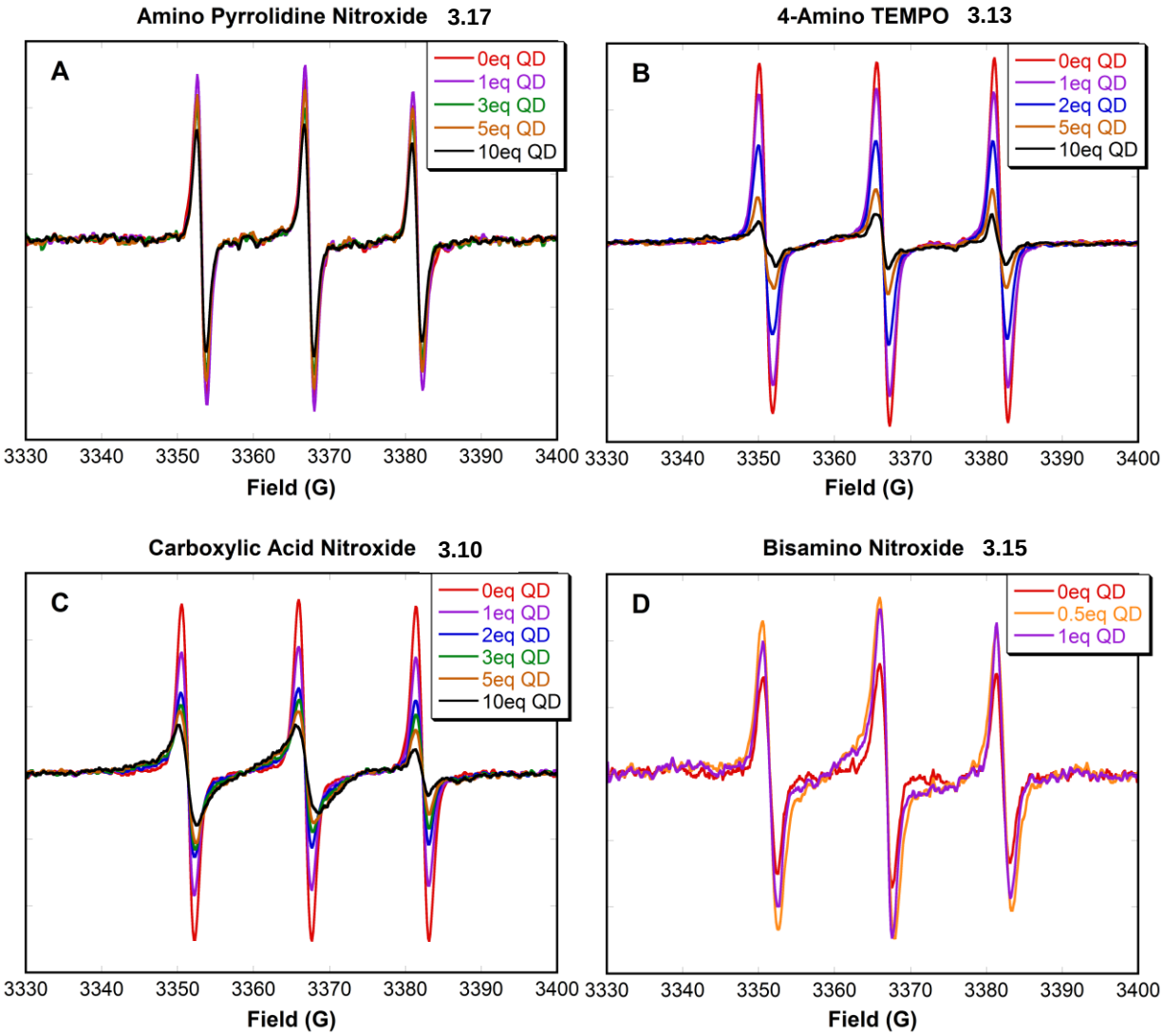


Figure 3.3A-D EPR spectra of nitroxides **3.17**, **3.13**, **3.10** and **3.15** (0.5 μM) in deaerated toluene upon successive addition of a solution of 3.7 nm CdSe QDs (note: eq. = equivalent)

To measure binding constants (K_b), saturation curves for 4-amino-TEMPO **3.13** and carboxylic acid nitroxide **3.10** interacting with CdSe QDs were obtained. The fraction of bound nitroxide (θ) is defined in **equation 3.1**, where [N] is the nitroxide concentration, and [QN] is the concentration of the QD-nitroxide complex.

$$\theta = \frac{[\mathrm{QN}]}{[\mathrm{N}] + [\mathrm{QN}]} \qquad \textbf{equation 3.1}$$

By applying the equation for the dissociation constant (K_d) from **equation 3.2**, where [Q] is the concentration of unbound CdSe QDs, an equation involving only [Q] and K_d is obtained, as shown in **equation 3.3**, assuming there is no cooperative effect.

$$K_d = \frac{[Q][N]}{[QN]} \qquad \textbf{equation 3.2}$$

$$\theta = \frac{[\mathrm{QN}]}{K_\mathrm{d}\frac{[\mathrm{QN}]}{[\mathrm{Q}]} + [\mathrm{QN}]} = \frac{1}{\frac{K_\mathrm{d}}{[\mathrm{Q}]} + 1} = \frac{[\mathrm{Q}]}{K_\mathrm{d} + [\mathrm{Q}]} \qquad \textbf{equation 3.3}$$

$$K_\mathrm{b} = \frac{1}{K_\mathrm{d}} \qquad \textbf{equation 3.4}$$

θ was determined using the relative peak heights at high field observed in the EPR spectra. The plots between θ and [Q] provided saturation curves for each nitroxide. When the curve is saturated, it is assumed that all nitroxide molecules are bound onto CdSe QD surfaces. The dissociation constants, K_d, were obtained by curve fitting of saturation curves as shown in **Figure 3.4** for 4-amino TEMPO **3.13**, **Figure 3.5** for carboxylic acid **3.10**, and **Table 3.1**. The binding constant, K_b, is the reciprocal

of K_d as defined in **eq. 3.4**. K_b values for 4-amino-TEMPO **3.13** and carboxylic acid nitroxide **3.10** are $(4 \pm 2) \times 10^5$ and $(2 \pm 1) \times 10^6$ M^{-1}, respectively. A relative error of 15% is assumed due to the inherent error in evaluating the QD concentrations.

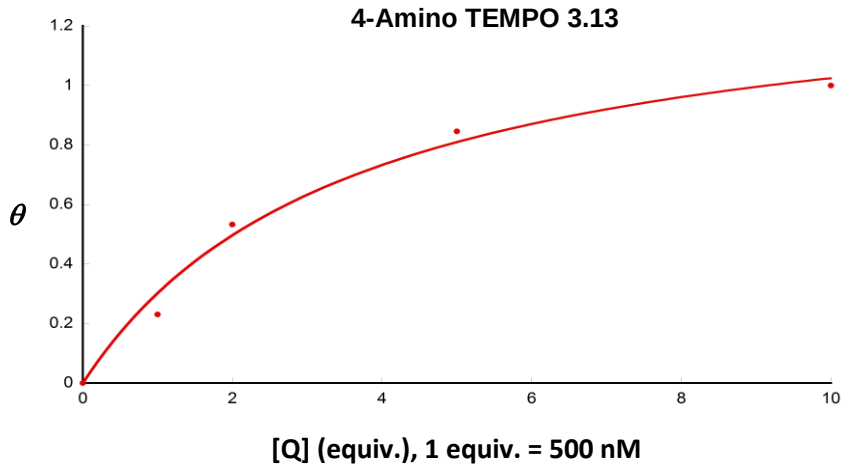


Figure 3.4 Nonlinear fit of the saturation curve for 4-amino TEMPO **3.13**

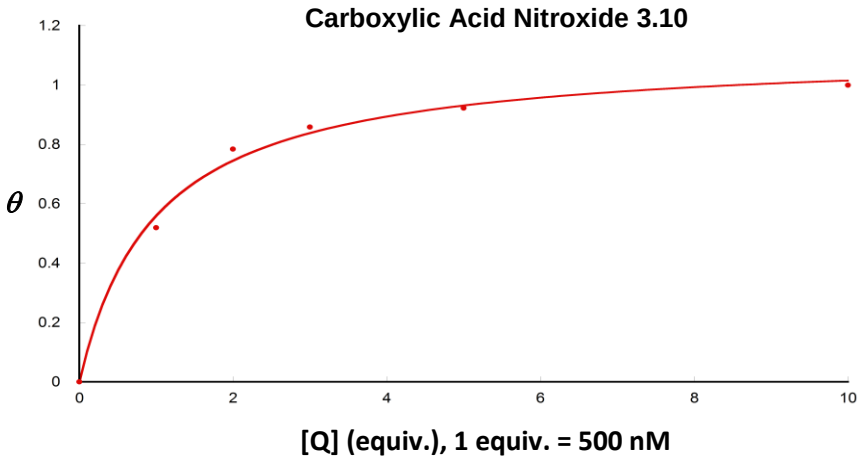


Figure 3.5 Nonlinear fit of the saturation curve for carboxylic acid nitroxide **3.10**

Table 3.1 Values obtained from nonlinear fit of the saturation curve for 4-amino TEMPO **3.13** and carboxylic acid **3.10**, where ***m*** = curve slope, K_d = dissociation constant, χ^2 = chi-square distribution, R^2 = coefficient of determination, and K_b = binding constant

$\theta = m*[Q]/(K_d + [Q])$				
	4-Amino TEMPO **3.13**		Carboxylic Acid Nitroxide **3.10**	
	Value	**Error**	**Value**	**Error**
m	1.395	0.14017	1.1166	0.037862
K_d	3.6152	0.88073	0.99536	0.13554
χ^2	0.0083251	-	0.0038351	-
R^2	0.99395	-	0.99723	-
K_b	$(4 \pm 2) \times 10^5$	-	$(2 \pm 1) \times 10^6$	-

Amino moieties on the surface are known to stabilize QDs.[28-30] In previous work, Scaiano *et al*. have shown that 4-amino-TEMPO **3.13** binds efficiently to 2.4-2.5 nm CdSe QDs with a binding constant of $(8 \pm 4) \times 10^6$ M^{-1}.[23] The binding constant obtained in this study for 4-amino-TEMPO **3.13** with 3.7 nm CdSe QDs is an order of magnitude lower than that previously reported. One should keep in mind that the 3.7 and 2.4-2.5 nm QDs were prepared using different procedures, including the use of tributylphosphine instead of trioctylphosphine for the larger QDs. Thus, the surface properties of these CdSe QDs are expected to be different as a result of variation in the synthetic conditions as well as particle size.[31] It is interesting that carboxylic acid-functionalized nitroxide **3.10** shows a greater affinity by an order of magnitude than the amino-substituted nitroxide **3.13**. The ability of carboxylic acids

to bind to the surface of CdSe nanoparticles[32] is not well explored and warrants further study.

Amino pyrrolodine nitroxide **3.17** was expected to show a binding affinity similar to that of 4-amino-TEMPO **3.13** because both bear amine functionalities. Bidentate bisamino nitroxide **3.15** was expected to bind more strongly to the QD surface than the monoamine counterpart. Unexpectedly, solutions of nitroxide **3.17** and **3.15** showed large discrepancies between the known molarities and the concentrations determined by EPR when calibrated using TEMPO as a standard. In the case of amino pyrrolidine nitroxide **3.17**, the difference between the two concentrations was a factor of 4. Addition of 10 equivalents (based on EPR nitroxide calibration) of QDs was not enough to produce a significant decrease in the EPR signal (**Figure 3.3A**, black line). Bisamino nitroxide **3.15** showed an entire order of magnitude discrepancy between the known molarity and the calibrated concentration, and an initially puzzling increase in the EPR signal intensity upon addition of QDs (**Figure 3.3D**) (*vide infra*). For all four nitroxides, the purities of the nitroxide samples were confirmed by NMR of the corresponding hydroxylamines (reduced in situ using phenylhydrazine). Before EPR experiments, the nitroxide samples were oxidized with PbO_2 and air to ensure that the entire sample was nitroxide rather than hydroxylamine. The lower apparent concentration of nitroxide

by EPR implies that there is an interaction between nitroxides in solution. This is discussed further in the next section

3.3.2 Competition and Low Temperature Studies

Competition studies were performed by the addition of competitive ligands with similar binding functionalities. Benzylamine and 4-phenylbutyric acid were used as competitors of amine and carboxylic acid-functionalized nitroxides **3.13** and **3.10**, respectively. In the first set of competition experiments, CdSe QDs were added to a mixture of nitroxide and a large excess (6×10^5 equivalents) of competitor. EPR spectra were taken at $t = 0$ (immediately upon addition of the QDs) and $t = 4$ h. The EPR signal intensity was expected to decrease upon addition of the QDs, but not as much as in the absence of the competitor. This is due to the benzylamine competing with 4-amino-TEMPO **3.13** for binding sites on the quantum dot. However, the EPR signal of a mixture of 4-amino-TEMPO **3.13**, benzylamine, and QDs (**Figure 3.6A**, red line) increased above the original signal of 4-amino-TEMPO **3.13** (**Figure 3.6A**, black line). After 4 h, the intensity had not changed (**Figure 3.6A**, blue line). **Figure 3.6B** shows the results of a similar competition between carboxylic acid nitroxide **3.10** and 4-phenylbutyric acid. An increase in signal intensity was again observed (**Figure 3.6B**, red line), but was not as pronounced as that of 4-amino-TEMPO **3.13**. After 4 h, the intensity dropped below the original nitroxide signal (**Figure 3.6B**, blue line),

indicating that eventually some of the carboxylic acid nitroxide **3.10** became bound to the QD surface.

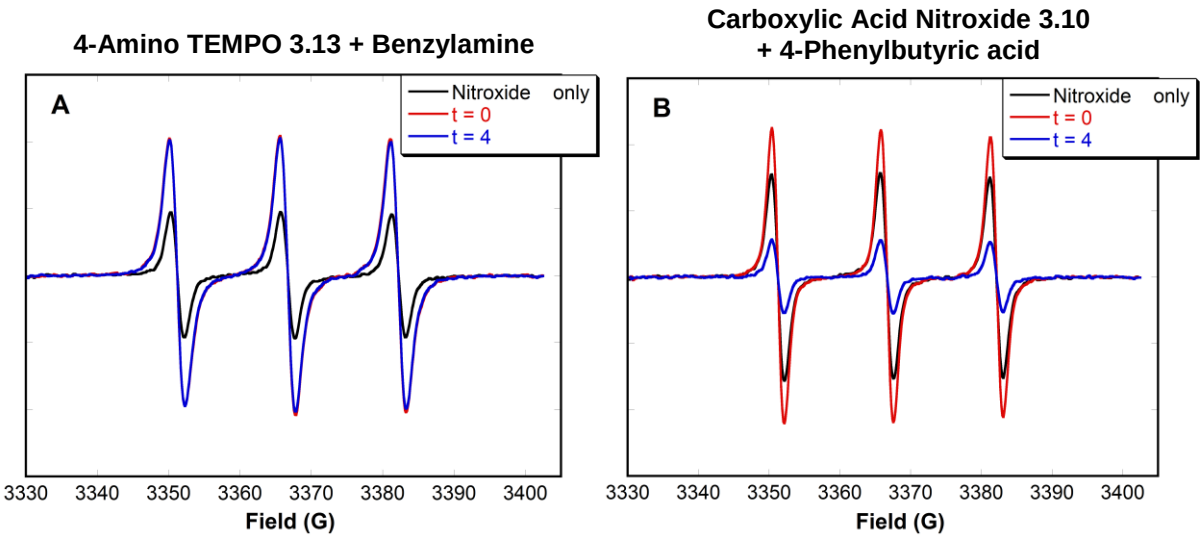


Figure 3.6 EPR spectra of a mixture of (**A**) 4-amino-TEMPO **3.13** or (**B**) carboxylic acid nitroxide **3.10** (0.5 μM) with CdSe QDs (2 μM) and a large excess of the corresponding competitor (6×10^5:1 moles of competitor/nitroxide) in deaerated toluene. Spectra were taken at t = 0 and 4 h.

In the second set of competition experiments, EPR spectra of a mixture of nitroxide and CdSe QDs were taken at t = 0 and t = 4 h in the absence of competitor. A large excess (6×10^5 equivalents) of competitor was then added at t = 4 h, and the spectra were taken at t = 8 h. In the case of 4-amino-TEMPO **3.13**, upon addition of CdSe QDs at t = 0 h, the EPR intensity decreased as expected (**Figure 3.7A**, red line) and continued to decrease as presumably more nitroxides became bound by t = 4 h (**Figure 3.7A**, blue line). However, four hours after the addition of benzylamine, at t

= 8 h, the signal intensity increased dramatically (**Figure 3.7A**, purple line). This increase in signal was similar to that seen in the first set of competition experiments. In contrast, carboxylic acid nitroxide **3.10** showed the expected behavior: the signal intensity decreased upon addition of CdSe QDs and continued to do so at *t* = 4 h (**Figure 3.7B**, red and blue lines). Four hours after 4-phenylbutyric acid was added (*t* = 8 h), the EPR intensity had increased (**Figure 3.7B**, purple line), but not beyond the initial value. These results indicate that some of the nitroxides **3.10** on the QD surface were displaced by the added competitor. Addition of a large excess (6×10^5

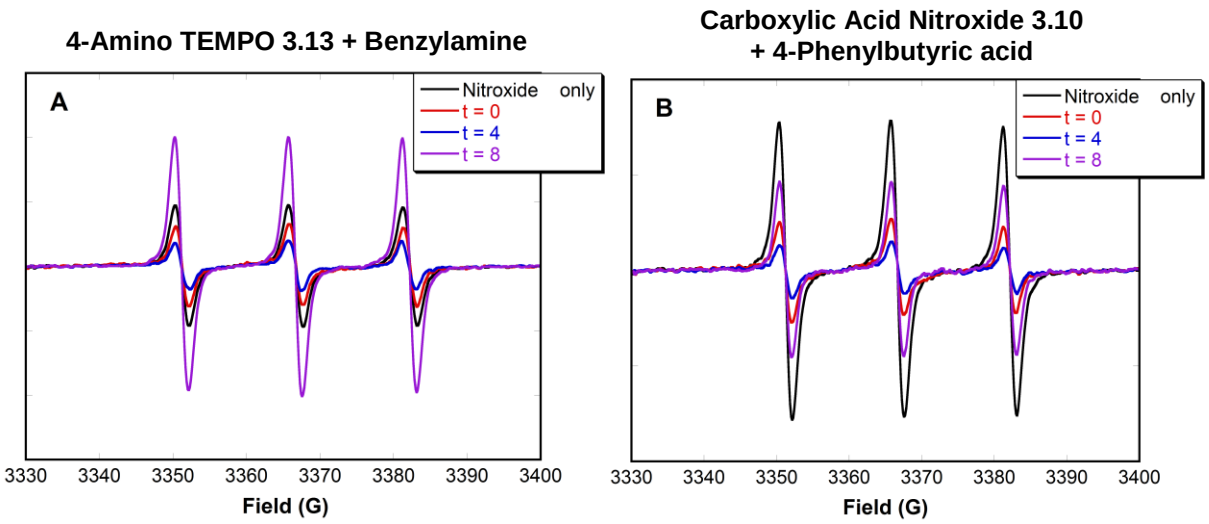


Figure 3.7 EPR spectra of a mixture of (**A**) 4-amino-TEMPO **3.13** or (**B**) carboxylic acid nitroxide **3.10** (0.5 μM) with CdSe QDs (2 μM) in deaerated toluene. Spectra were taken at *t* = 0 and 4 h. At *t* = 4 h, a large excess of their corresponding competitors (6×10^5:1 moles of competitor/nitroxide) was added, and spectra were taken at *t* = 8 h.

equivalents) of benzylamine to bisamino nitroxide **3.15** (in the absence of CdSe QDs) also resulted in an increase in the EPR signal intensity, similar to that observed with 4-amino-TEMPO **3.13**; however, bisamino nitroxide **3.15** gave an even more dramatic change (**Figure 3.8**).

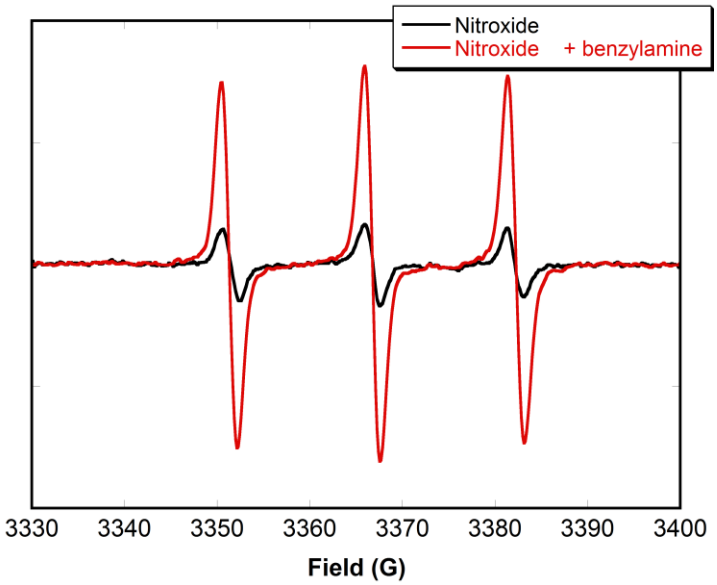


Figure 3.8 EPR spectra of bisamino nitroxide **3.15** (0.5 μM) in deaerated toluene before and after the addition of a large excess benzylamine (6×10^5:1 moles of benzylamine:nitroxide **3.15**)

As a control, the EPR signal of the nonfunctionalized nitroxide TEMPO did not show any effect upon the addition of benzylamine (**Figure 3.9**), indicating that the functional groups attached to the nitroxide molecules play an important role in the unexpected signal enhancement. It is postulated that this behavior is due to significant intermolecular hydrogen bonding between the nitroxide oxygen and the

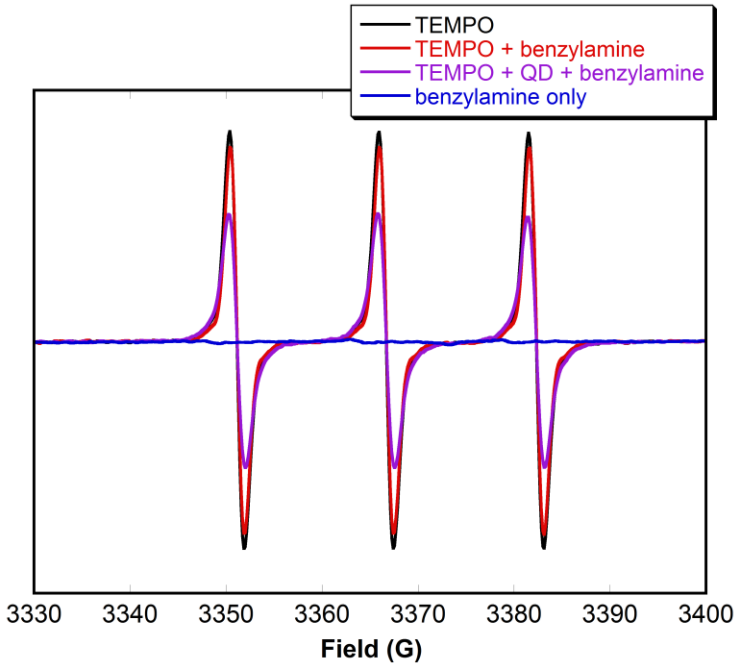


Figure 3.9 EPR spectra of TEMPO (0.5 μM) in deaerated toluene before and after the addition of a large excess of benzylamine (6×10^5:1 moles of benzylamine:TEMPO) and CdSe QDs (4 μM)

amine or carboxylic acid functional groups in the nonprotic solvent toluene. Indeed, there is precedence for this type of intermolecular hydrogen bonding between functionalized nitroxides being observed by EPR, even for fairly dilute solutions of nitroxides containing carboxylic acid,[33-35] lactam,[34] hydroxyl,[36] and oxime groups.[37] EPR evidence for intramolecular hydrogen bonding has also been reported in the case of hydroxy-substituted nitroxides.[38-41] Nitroxides also form hydrogen bonds with a variety of other proton-donating molecules.[42-44] By being in close proximity during hydrogen bonding, the nitroxide moieties can interact, thus broadening and

diminishing the intensity of the EPR signal. By adding benzylamine, the nitroxide-nitroxide associations are replaced by nitroxide-benzylamine hydrogen-bonded complexes, restoring the nitroxides to their monomeric forms, with concomitant return of the EPR signals to their expected intensities.

Additional evidence for intermolecular hydrogen bonding with 4-amino-TEMPO **3.13** and bisamino nitroxide **3.15** was provided by EPR measurements in *p*-xylene at 125 K (**Figure 3.10A**-**B**). At this temperature, the media is a glass, resulting in limited exchange interactions. Thus, the major effect on EPR signals at this cold temperature comes from dipolar interactions through space, predominated by

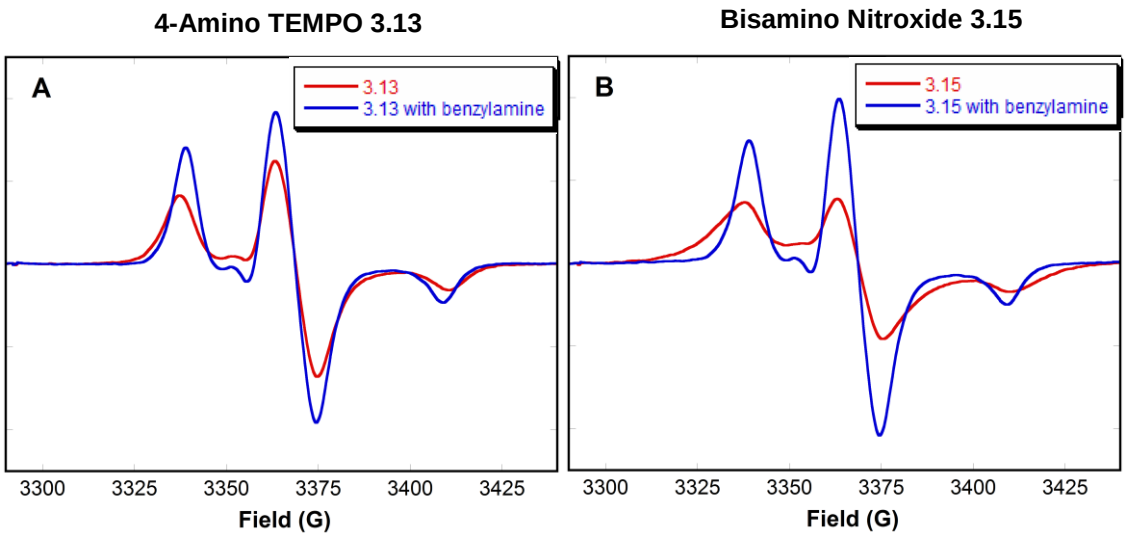
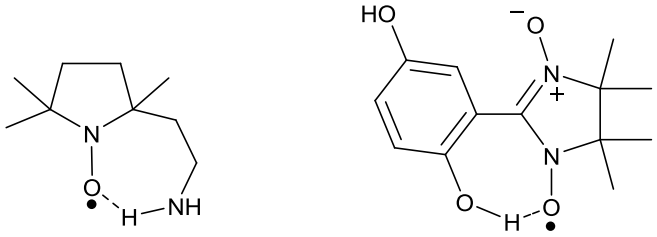


Figure 3.10A-B EPR spectra of a mixture of 4-amino-TEMPO **3.13** (50 μM) or bisamino nitroxide **3.15** (200 μM) with and without benzylamine (6×10^5:1 moles of benzylamine/nitroxide) in deaerated *p*-xylene. Spectra were recorded at 125 K in *p*-xylene.

hydrogen bonding. Without benzylamine, both nitroxide EPR signals were significantly broadened (red lines), indicating that nitroxide free radicals self-associate, resulting in spin-spin coupling interactions. Upon addition of benzylamine, the EPR peaks became sharper and stronger in intensity (blue lines), resulting from interruption by the benzylamine of self-association. This phenomenon of hydrogen bonding explains the discrepancy between the known molarity and the calibrated concentrations of the nitroxides as well as the increase in the EPR signal intensity beyond the original level when the competitor was added. In solution, EPR hyperfine lines from the nitroxide dimers or multimers are significantly broadened and thus, become silent relative to the monomer species. The EPR signal of amino pyrrolidine nitroxide **3.17** showed only small changes upon addition of CdSe QDs, presumably due to the seven membered-ring formed by an intramolecular hydrogen bond between the nitroxide oxygen and the tethered amine, as shown in **Figure 3.11**. This could interfere with bonding of the amine to the surface of CdSe quantum dots. Paola *et al.* observed a similar intramolecular hydrogen bonding between a nitroxide oxygen and a phenolic OH, resulting in a seven-membered ring (**Figure 3.11**).[45] The most dramatic effect of hydrogen bonding occurs with bisamino nitroxide **3.15**, as bidentate intermolecular hydrogen bonding is possible. Because association constants are derived from the equilibrium between the monomer nitroxides and

the QD bound species, the monomer concentrations were determined from integration of the sharp line EPR spectra.



Amino Pyrrolidine Nitroxide **3.17** Paola's Nitroxide

Figure 3.11 Seven membered-rings formed by an intramolecular hydrogen bond between a nitroxide oxygen and a proton donor

3.3.3 Time Studies

A series of time studies were performed on the same sample via EPR and fluorescence spectroscopies to correlate the change in the amount of bound nitroxide with the change in fluorescence quenching. Spectra of a 1:4 mixture of carboxylic acid nitroxide **3.10** and CdSe QDs in toluene were taken every 30 minutes for 4 h. The decrease in the EPR peak intensity showed that the free nitroxides continued to convert into bound species over the 4 h period (**Figure 3.12A**). The signal was still changing at the end of 4 h, indicating that equilibrium had not yet been reached. Similarly, fluorescence spectra showed a decrease in intensity over the 4 h period (**Figure 3.12B**), resulting from an increase in fluorescence quenching as more nitroxides bonded to the QD surface. Again, the process had not reached a plateau at the end of 4 h. This demonstrates a strong correlation between binding

affinity and quenching efficiency, which although not completely linear, does follow the same trend. This experiment also implies that the measurements used for the determination of the binding constant were taken significantly before the system reached equilibrium.

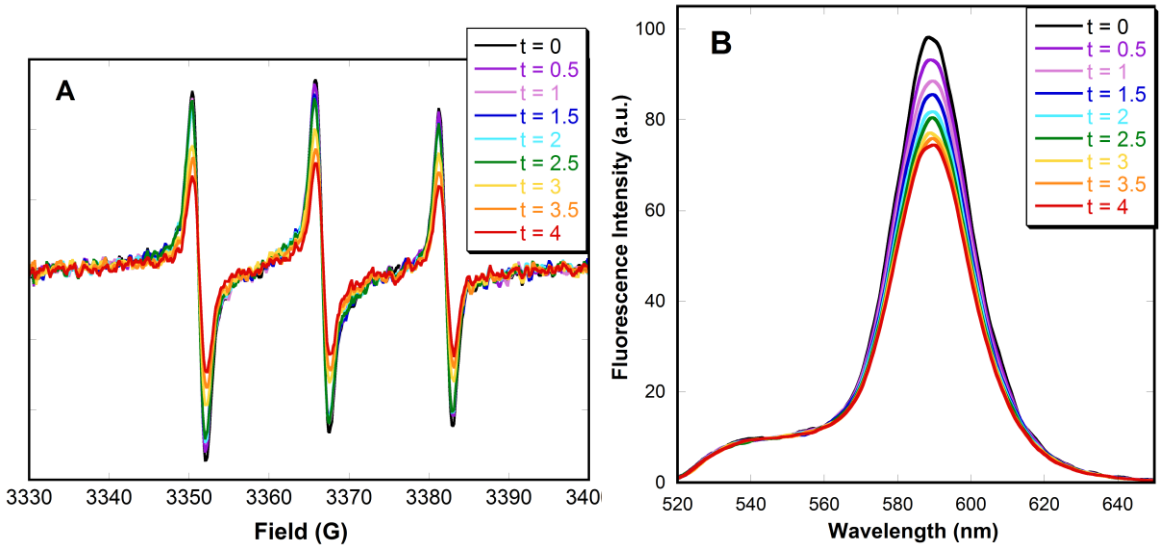


Figure 3.12 (**A**) EPR and (**B**) fluorescence spectra of carboxylic acid nitroxide **3.10** (0.5 μM) with CdSe QDs (2 μM) in deaerated toluene. Spectra were taken every 30 minutes for 4 hours.

To determine how this affects the value of the binding constant, EPR spectra of carboxylic acid nitroxide **3.10** with different concentrations of CdSe QDs were taken after each aliquot was allowed to equilibrate for 24 h. The signal intensities were greatly reduced (**Figure 3.13A**) as compared to those taken immediately after the addition of QDs (**Figure 3.3B**). As a control, the EPR signal intensities of

carboxylic acid nitroxide **3.10** without CdSe QDs after 24 h were unchanged (**Figure 3.13B**). This time requirement to reach equilibrium influences the determination of the binding constant. The binding constant for carboxylic acid nitroxide **3.10** calculated from the saturation curve taken after 24 h is $K_b = (8 \pm 4) \times 10^6\ M^{-1}$, four times greater than the previous value.

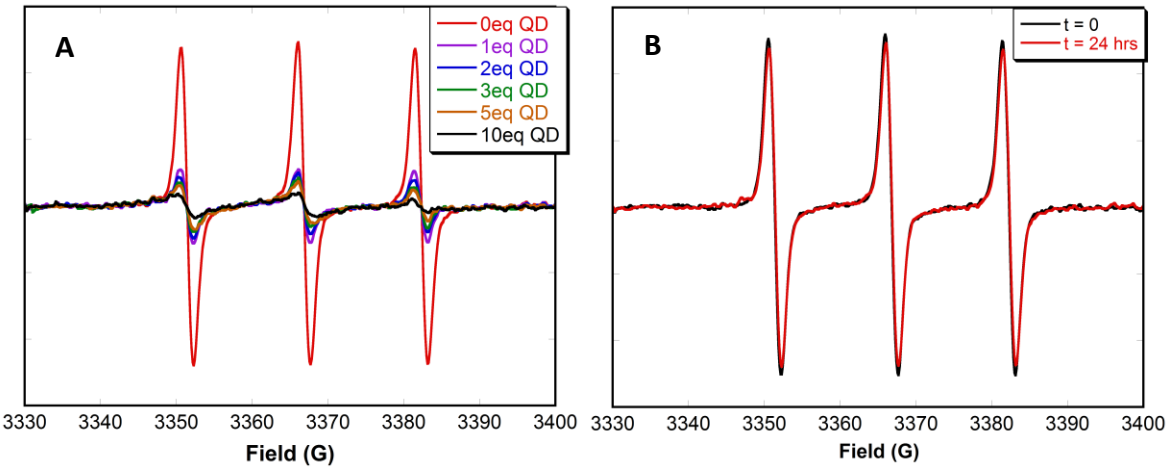
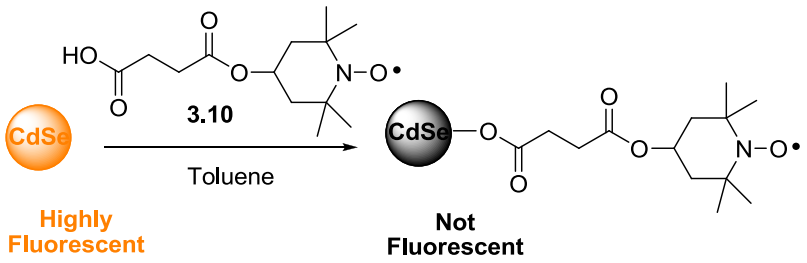


Figure 3.13 EPR spectra of carboxylic acid nitroxide **3.10** (0.5 μM) in deaerated toluene (**A**) with different concentrations of CdSe QDs (**B**) in the absence of CdSe QDs. Spectra were taken after each aliquot was allowed to equilibrate for 24 hours.

3.4 Fluorescence Quenching Efficiency

It has been reported that the quenching of CdSe QD fluorescence by 4-amino-TEMPO **3.13** occurs at a concentration at least 3 orders of magnitude lower than that required for TEMPO (see Chapter 2).[21, 22] Stern-Volmer plots for the fluorescence quenching by TEMPO are characterized by positive deviations from linearity, whereas negative deviations are observed in the case of 4-amino-TEMPO

3.13, attributed to amine binding to the QD surface. The addition of an excess of binding nitroxide to CdSe QDs resulted in a dramatic decrease in fluorescence that can be observed by the naked eye. For example, as illustrated in **Scheme 3.8** and **Figure 3.14**, QD fluorescence in the presence of carboxylic acid nitroxide **3.10** (on the left) was effectively quenched, but the vial in the presence of the non-binding nitroxide, TEMPO (in the middle) looked the same as the control in the absence of nitroxide (on the right). This indicated that binding by the carboxylic acid group to the QD surface was necessary for fluorescence quenching.



Scheme 3.8 Fluorescence of CdSe QDs was quenched after the addition of carboxylic acid functionalized nitroxide **3.10**.

Figure 3.14 Fluorescence of 5 μM CdSe QDs in toluene in the presence of (from left to right): carboxylic acid nitroxide **3.10** (2500:1 moles of nitroxide **3.10**:QDs), TEMPO (2500:1 moles of TEMPO:QDs), and no additive upon illumination with a TLC lamp at 366 nm

The emission spectra of CdSe QDs at λ_{max} = 591 nm in the absence and presence of increasing concentrations of all four functionalized nitroxides in **Figure 3.1** are shown in **Figure 3.15A-D**. Fluorescence intensities decreased as the concentration of nitroxide increased. Quenching was noticeable upon addition of the first equivalent of nitroxide, consistent with the very high binding constants for these QD-nitroxide complexes. At a high concentration of nitroxide, subsequent addition of additional nitroxide resulted in only a small decrease in photoluminescence. Scaiano *et al*.[21] have offered a satisfying explanation: at low concentration, nitroxides are able to bind easily by filling vacancies in the layer of ligands covering the QD surface. However, at high concentration, binding requires the displacement of existing ligands on the QD surface; subsequent substitution becomes increasingly more difficult. A control experiment was performed to show the dilution effect of added toluene on QD emission intensity (**Table 3.2**). The emission intensity was reduced by 36% and 50% after adding 1 mL and 2 mL of toluene, respectively, which correlates well with Beer-Lambert law (25% and 50% predicted). These results confirm that reduction of the emission intensity is mostly a result of nitroxide quenching.

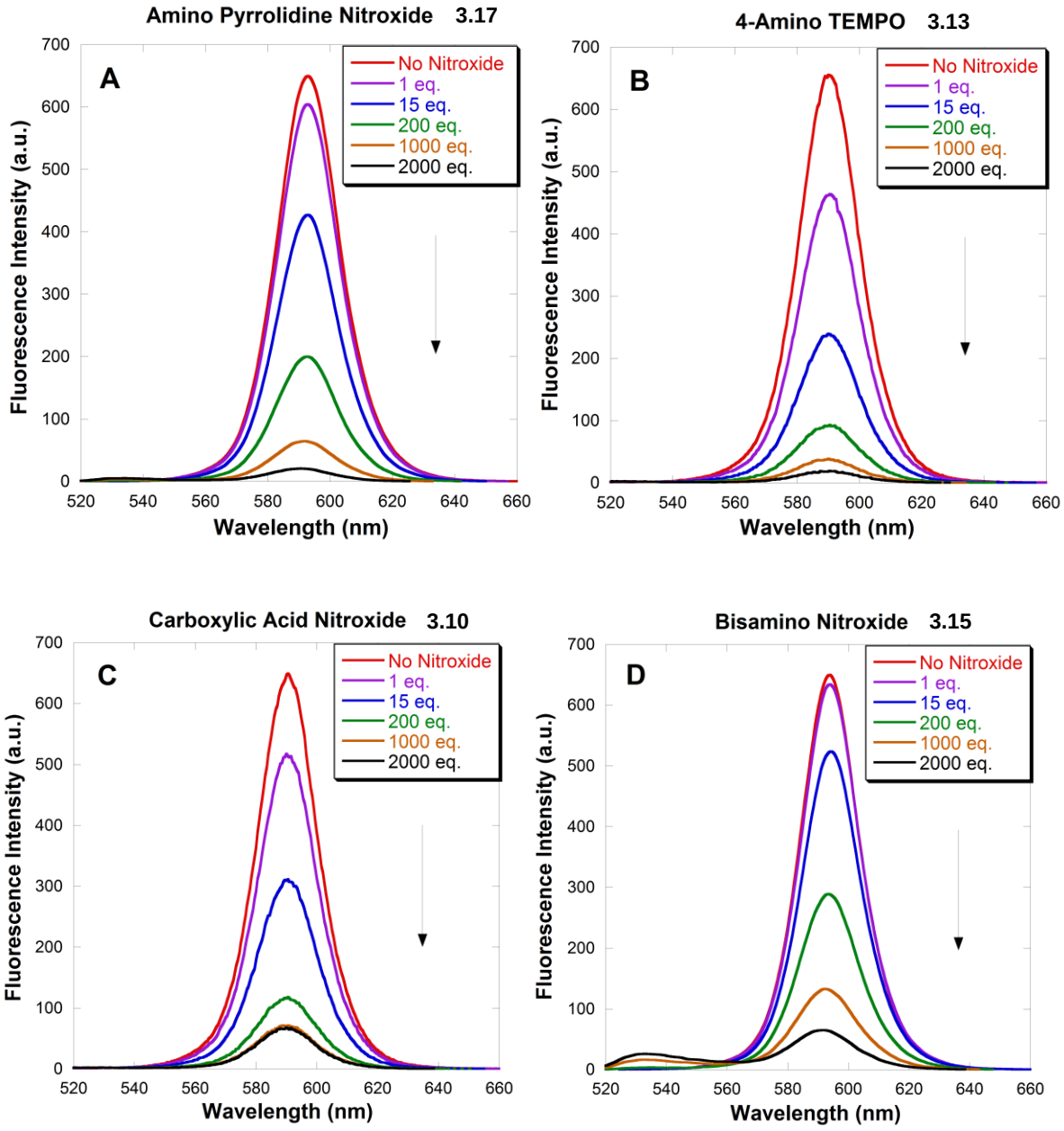


Figure 3.15A-D Fluorescence emission spectra (λ_{ex} = 390 nm) of toluene solutions of 3.7 nm CdSe QDs (0.4 μM) quenched by increasing amounts of added nitroxides (only 5 different amounts are shown). Spectra were taken 60 seconds after addition of each aliquot.

Table 3.2 Photoluminescence (PL) intensity and % PL reduction at λ_{max} 591 nm of CdSe QDs in toluene upon the addition of toluene

Volume of Added Toluene (mL)	PL Intensity	PL Reduction (%)
0	651.20	0
1	419.07	36
2	324.58	50

From the magnitude of the fluorescence intensity, it is evident that the emission of the CdSe QDs is quenched most effectively by 4-amino-TEMPO **3.13**, followed by carboxylic acid nitroxide **3.10** and amino pyrrolidine nitroxide **3.17**; quenching is least effective by bisamino nitroxide **3.15**. In all cases, addition of 2000 equiv of nitroxide was not sufficient to suppress the fluorescence completely. A slight blue shift was observed with each addition of nitroxide solution. This may be attributed to a small decrease in the QD size, possibly due to dissolution upon dilution.

Quenching efficiency is conveniently measured by the concentration of nitroxide required to achieve a 50% reduction in the emission intensity, as shown in **Table 3.3**. 4-Amino TEMPO **3.13** is three times more effective as a quencher than carboxylic acid nitroxide **3.10**, which is, in turn, an order of magnitude more effective than amino pyrrolidine nitroxide **3.17** and bisamino nitroxide **3.15**. These results are inconsistent with the binding affinities for 4-amino-TEMPO **3.13** and

carboxylic acid nitroxide **3.10**; instead the quenching efficiencies correspond to the *proximity* of the nitroxide radicals to the QD surfaces.

Table 3.3. Concentrations of nitroxides required to reduce the fluorescence of 0.4 μM CdSe QDs in toluene by 50%

Nitroxides	Concentration for $I_o/I = 2$ (M)
Amino Pyrrolidine **3.17**	1.9×10^{-5}
4-Amino TEMPO **3.13**	2.0×10^{-6}
Carboxylic Acid **3.10**	6.3×10^{-6}
Bisamino **3.15**	5.7×10^{-5}

Molecular mechanics calculations (MM2) were used to estimate lengths from the nitroxide oxygen atom to the ligand functionality: for amino pyrrolidine nitroxide **3.17**, 4-amino TEMPO **3.13**, carboxylic acid nitroxide **3.10**, and bisamino nitroxide **3.15** in **Figure 3.1**, the distances were 4.7, 5.6, 8.0, and 11.1 Å, respectively. Although carboxylic acid nitroxide **3.10** has a higher binding affinity to the QDs than 4-amino-TEMPO **3.13**, nitroxide **3.13** holds the nitroxide moiety closer to the QD surface. The long tether of bisamino nitroxide **3.15** holds the nitroxide moiety remote to the QD surface and hence, is the least effective quencher. A similar distance dependence has been observed in the intramolecular quenching between nitroxides and organic dyes.[19, 46] Amino pyrrolidine nitroxide **3.17** was expected to be an excellent quencher due to the short and flexible tether between the primary

amine and the nitroxide; however intramolecular hydrogen bonding interactions dramatically diminishes binding and/or quenching efficiency such that it is even less effective than carboxylic acid nitroxide **3.10**. Thus nitroxide quenching efficiency depends on both the binding affinity *and* the proximity of the nitroxide moiety to the QD surface; the proximity effect dominates. Moreover, hydrogen bonding also contributes to the quenching efficacy.

The quenching efficiency can also be analyzed by plotting the fluorescence intensity at the maximum wavelength as a function of nitroxide concentration in a Stern-Volmer fashion, as shown in **Figure 3.16A**. Deviations from linearity are attributed to a combination of static and dynamic quenching and to the differential binding of the quenchers to the QD surface.[47] Positive deviations (upward curvature) are predicted by several related models, including the transient effect model[48] for diffusion-controlled reactions; the sphere of action model,[47] in which quenching results from the quencher molecule lying immediately adjacent to the fluorophore at the moment of excitation; the dark complex model[49] relying on proximity but no specific physical contact; and the distance-dependent quenching model.[50] Negative deviations (downward curvature) have been observed in the fluorescence quenching of CdSe QDs by *n*-butylamine[51, 52] as a hole acceptor and by boronic acid substituted viologen quenchers.[53] Upward and downward curvatures have been reported for

the quenching of CdSe QD fluorescence by nonbinding and binding nitroxides, respectively.[22]

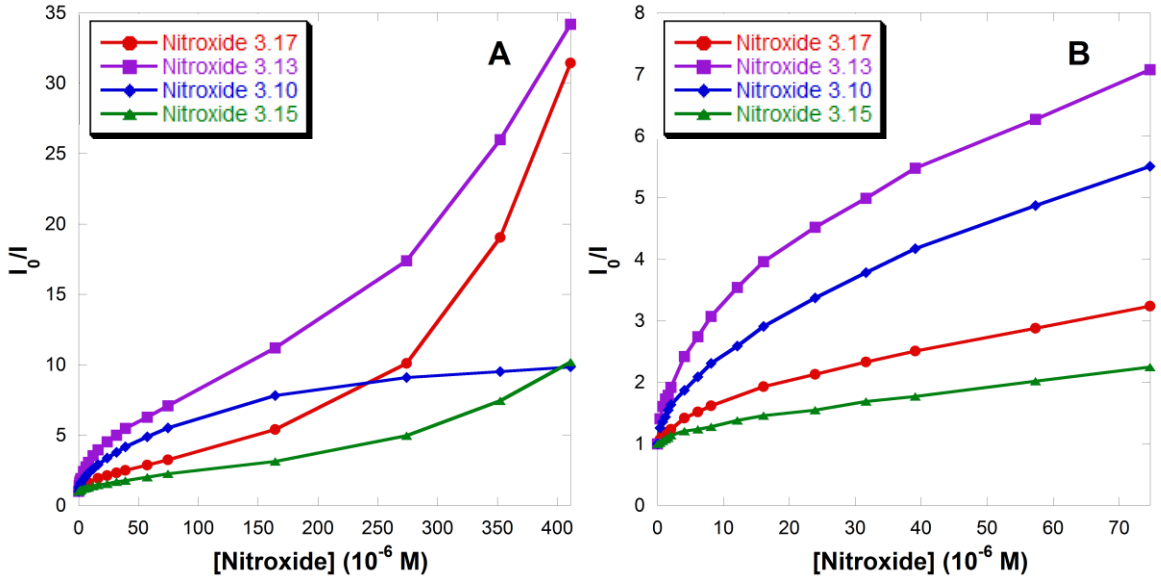


Figure 3.16 (A) Stern-Volmer plots of fluorescence quenching by nitroxides at the emission maximum of 594 nm. **(B)** Enlargement for [nitroxide] < 77 μM; I = observed fluorescence intensity, I_o = fluorescence intensity with no nitroxide

Because dynamic quenching also contributes to fluorescence quenching by the ligand-bearing nitroxides,[54] the downward curvatures observed in **Figure 3.16B** are likely due to a combination of dynamic and static quenching, whereas the upward curvature is associated only with dynamic quenching. The data showing downward curvatures (data at low concentrations for pyrrolidine nitroxide **3.17**, 4-amino TEMPO **3.13**, bisamino nitroxide **3.15** and the entire curve for carboxylic acid

nitroxide **3.10** in **Figure 3.16B**) can be fit by a "multibinding-site" model: **eq. 3.5** as reported by Guo *et al*.[54] (**Figures 3.17A**, **3.18A**, **3.19**, and **3.20A**), where K_D is the dynamic quenching constant, K_S is the static quenching constant, [nitroxide] is concentration of the nitroxide, and *n* is the average number of immediately available empty binding sites on the QD surface. This modified Stern-Volmer model gives R^2 values higher than 0.99, a much better fit than the "sphere of action" model.[47]

$$\frac{I_0}{I} = 1 + K_D[\text{nitroxide}] + K_S[\text{nitroxide}]^n + K_D K_S[\text{nitroxide}]^{n+1} \qquad \textbf{eq. 3.5}$$

An exponential dependence described by **eq. 3.6** is observed for the upward curvatures seen at high concentrations for pyrrolidine nitroxide **3.17**, 4-amino TEMPO **3.13**, and bisamino nitroxide **3.15**, as previously reported for the nonbinding nitroxide TEMPO,[21] where *A* is the amplitude, α is the dynamic quenching constant and [nitroxide] is concentration of nitroxide (**Figures 3.17B**, **3.18B**, and **3.20B**).

$$\frac{I_0}{I} = Ae^{\alpha[\text{nitroxide}]} \qquad \textbf{eq. 3.6}$$

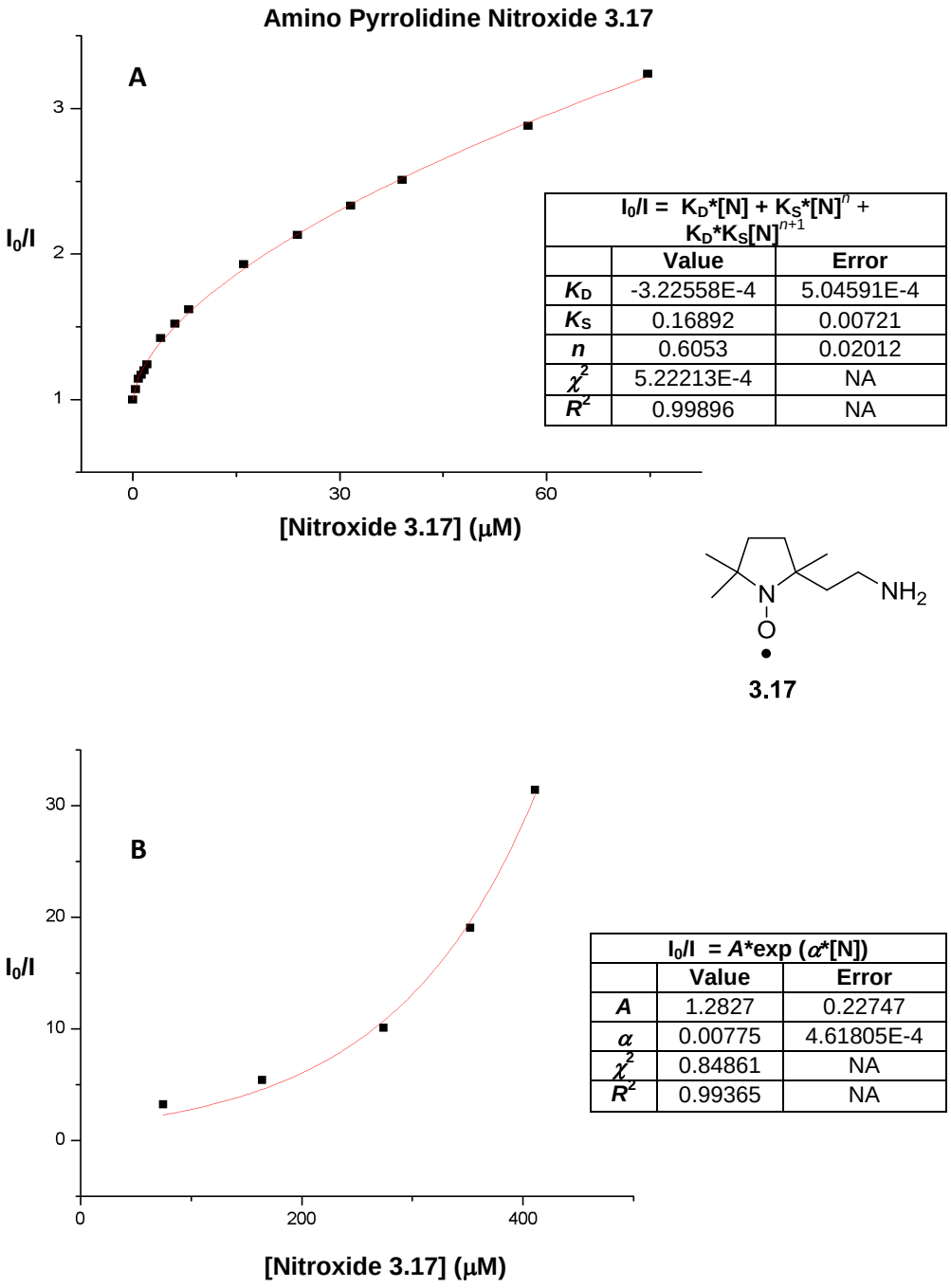


Figure 3.17 Nonlinear curve fit of (**A**) the downward curvature and (**B**) the upward curvature in the Stern-Volmer plot of amino pyrrolidine nitroxide **3.17**

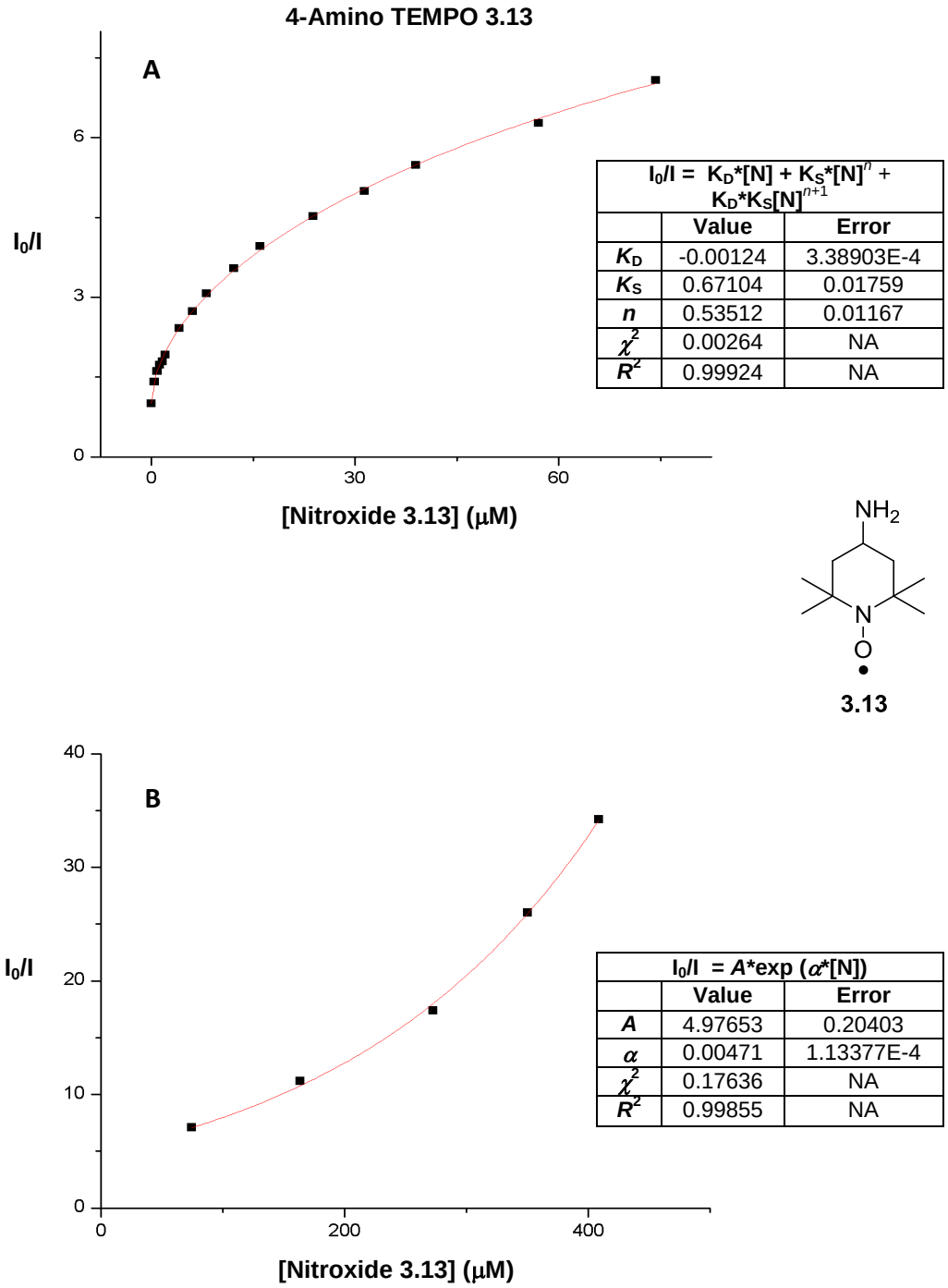


Figure 3.18 Nonlinear curve fit of (**A**) the downward curvature and (**B**) the upward curvature in the Stern-Volmer plot of 4-amino TEMPO **3.13**

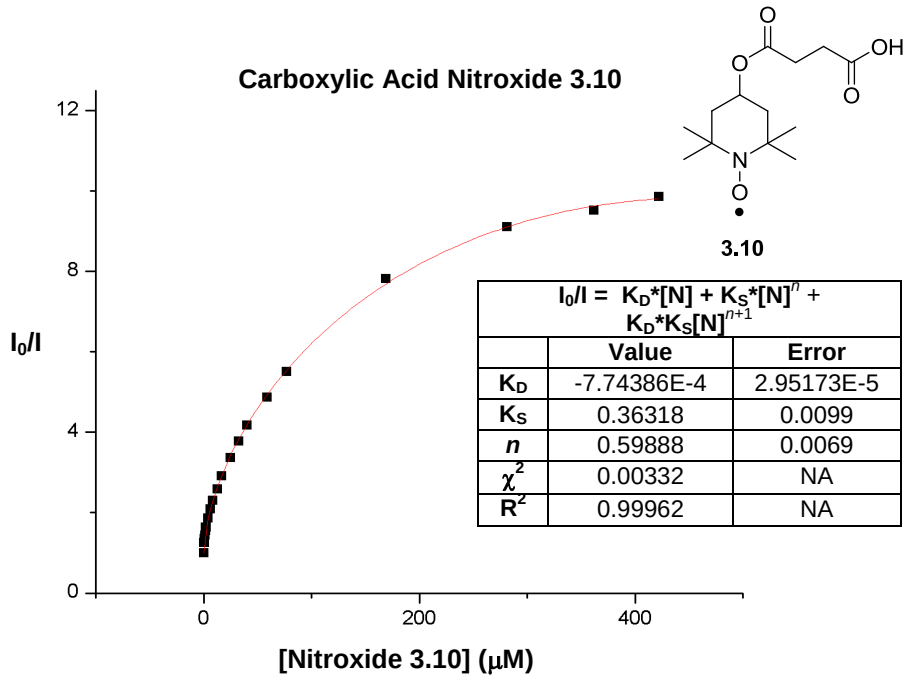
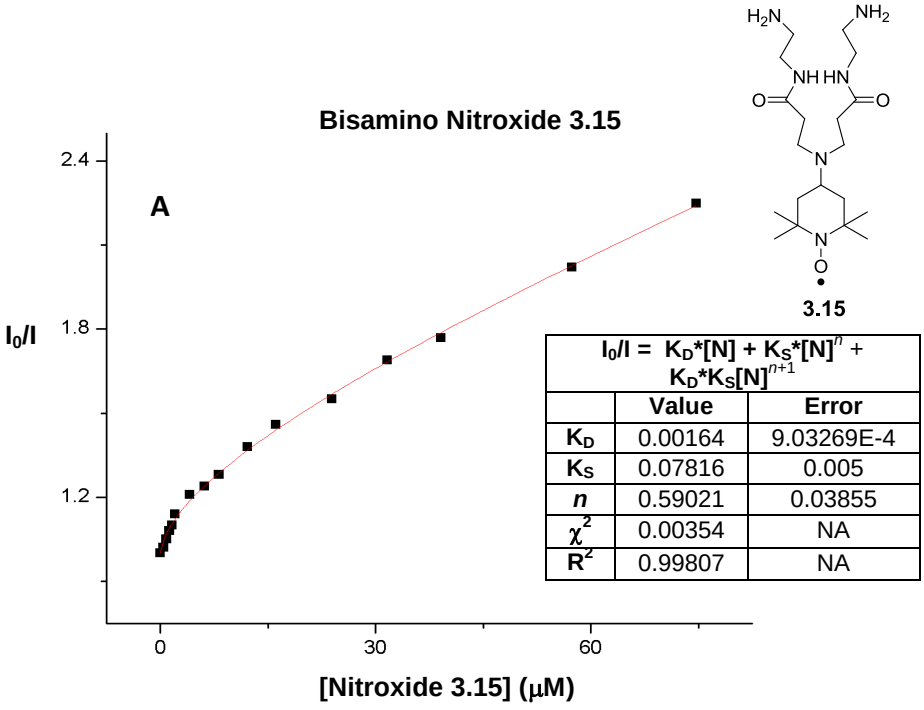


Figure 3.19 Nonlinear curve fit of the downward curvature and in the Stern-Volmer plot of carboxylic acid nitroxide **3.10**



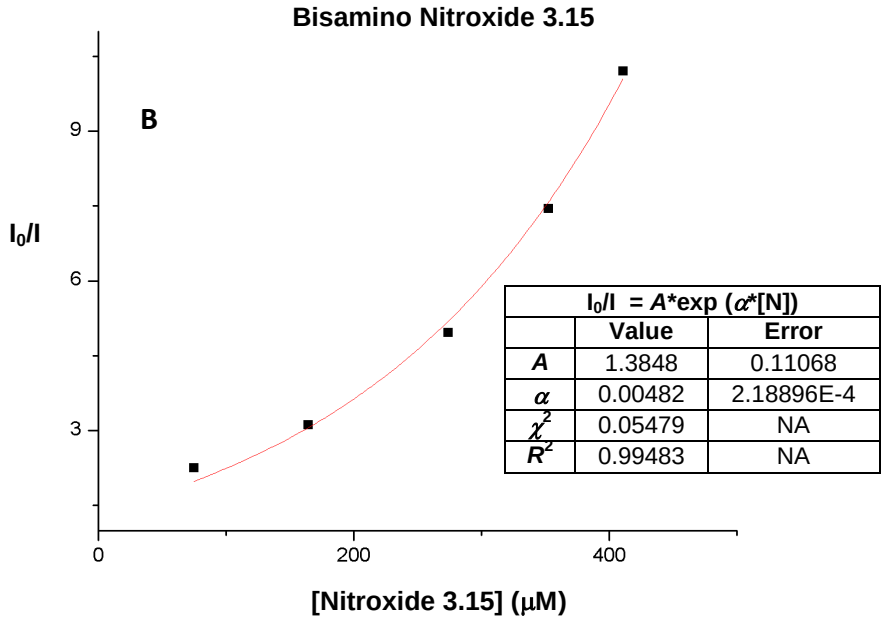


Figure 3.20 Nonlinear curve fit of (**A**) the downward curvature and (**B**) the upward curvature in the Stern-Volmer plot of bisamino nitroxide **3.15**

As summarized in **Table 3.4**, it is evident that fluorescence quenching by these ligand bearing nitroxides is predominantly due to a static quenching mechanism, because K_S values are much greater than K_D values. 4-Amino-TEMPO **3.13** has a higher value of K_S than that of carboxylic acid nitroxide **3.10** due to the close proximity of the radical when it is bound to the QD surface. The low K_S value for amino pyrrolidine nitroxide **3.17** is due to intramolecular hydrogen bonding between the nitroxide oxygen and the amine tethered by a flexible linker. The dynamic quenching efficiencies of amino-substituted nitroxides **3.17** and **3.13** are also indicated by the α values at high concentrations, as observed by the upward

curvature of the Stern-Volmer plots. This may be understood in terms of the great mobility of amino pyrrolidine nitroxide **3.17** and 4-amino-TEMPO **3.13**. The enhanced rotation of small molecules facilitates fluorescence quenching, even when the nitroxides are not bound to the QD surface. The total effect makes 4-amino-TEMPO **3.13** the most effective quencher, followed by carboxylic acid nitroxide **3.10** and amino pyrrolidine nitroxide **3.17**, respectively.

Table 3.4 Dynamic quenching constants (K_D) and static quenching constants (K_S) of nitroxides, average number of immediately available empty binding sites (n) on the QD surface, and dynamic quenching constants at high concentration (α) of nitroxides

Nitroxides	K_D **(M^{-1})**	K_S **(M^{-1})**	**binding sites, *n***	α **(M^{-1})**
Amino Pyrrolidine **3.17**	322	1.69×10^5	0.60	7750
4-Amino TEMPO **3.13**	1240	6.71×10^5	0.54	4710
Carboxylic Acid **3.10**	774	3.63×10^5	0.60	-
Bisamino **3.15**	1640	7.82×10^4	0.59	4820

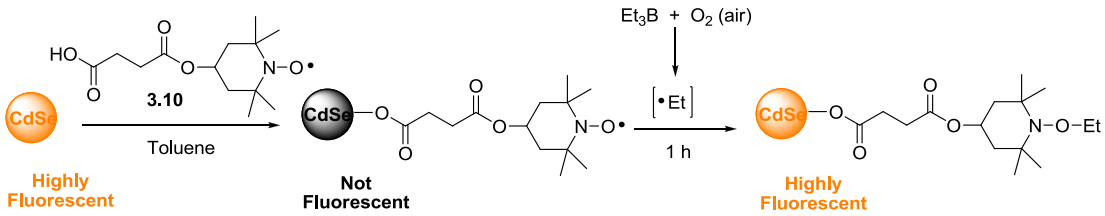
Bisamino nitroxide **3.15** has the smallest K_S and the largest K_D values. The two long chains of the bisamine make nitroxide **3.15** sterically large; as a result, the nitroxide has limited accessibility to the QD surface, resulting in the smallest K_S. Similar examples have been previously reported of hindered access to a semiconductor surface resulting in decreasing quenching effectiveness.[55, 56] Apparently, the first molecule of bisamino nitroxide **3.15** binds to an available empty

site ($n \approx 1$) on the QD surface; following this, a few more nitroxides can bind by exchange with surrounding ligand molecules. Subsequent bisamines find it difficult to access the QD surface. The static quenching still dominates in this case due to the tight binding of the bisamine bidentate functionality. However, dynamic quenching also plays a significant role at low concentrations, as observed by the greatest K_D value. Overall, bisamino nitroxide **3.15** is the least effective quencher in this study.

The values of α obtained from the upward curved regions in **Figure 3.16A** using **eq. 3.6** are 7750, 4710, and 4820 M^{-1} for pyrrolidine nitroxide **3.17**, 4-amino TEMPO **3.13**, bisamino nitroxide **3.15**, respectively. At higher concentrations, quenching is dominated exclusively by the dynamic process, which does not require binding of nitroxides to the QDs. Thus the α values for nitroxides **3.17**, **3.13**, and **3.15** are all of the same magnitude. Amino pyrrolidine nitroxide **3.17** has the largest value due to the small size of this molecule, facilitating the dynamic quenching. The average number of immediately available empty binding sites on the QD surface n for all four nitroxides is consistently a little less than one, which is close to the reported values of 1 and 1.12 for 2.4-2.5 nm CdSe[23] and 2.8 nm CdTe QDs,[54] respectively, conjugated with 4-amino-TEMPO **3.13**. This indicates that to bind additional nitroxides, subsequent nitroxide molecules need to displace existing ligands on the QD surface. The α values are much smaller than K_S, indicative of limited accessibility of a second site on the QD surface.

3.5 Fluorescent Recovery

To determine if fluorescence can be restored after quenching, several methods of converting the nitroxide moiety to a hydroxylamine or alkoxyamine were investigated: the addition of phenylhydrazine, sodium ascorbate (vitamin C),[57, 58] α-tocopherol (vitamin E),[59] glutathione,[60] 5-hydroxynaphthoquinone (juglone),[61] 2-hydroxy-1,4-naphthoquinone (lawsone),[61] azo-bis-isobutyronitrile (AIBN) at 60 °C,[23] and dimethylsulfoxide (DMSO) in the presence of hydrogen peroxide and iron(II) sulfate.[62] None of these reagents worked, presumably due to the destruction of the CdSe QDs. In order to successfully restore the QD fluorescence, the quenched CdSe QD-carboxylic acid nitroxide **3.10** complex was exposed to ethyl radicals generated from triethylborane in the presence of the air[63] (**Scheme 3.9** and **Figure 3.21**). To confirm this chemistry, the trapping of ethyl radical with the nitroxide 4-hydroxy-2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPOL) was carried out on a preparative scale using a longer reaction time (**Scheme 3.10**) to give the ethoxyamine **3.18** in 52% isolated yield. It is evident that the recovery of QD fluorescence resulted from the disappearance of nitroxide radical by the formation of ethoxyamine; however the fluorescence was not completely restored using this trapping reaction, presumably due to incomplete reaction.



Scheme 3.9 Fluorescence of the quenched CdSe QD-carboxylic acid nitroxide **3.10** complex was restored by treating with ethyl radicals generated from triethylborane in the presence of the air.

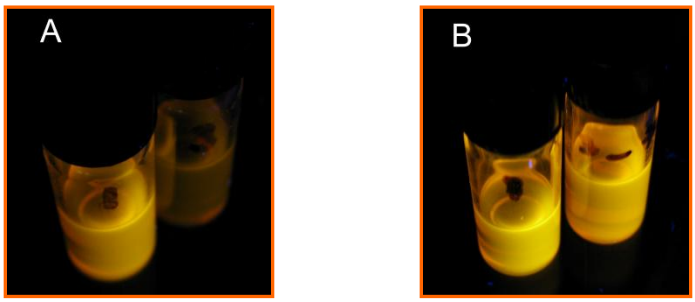
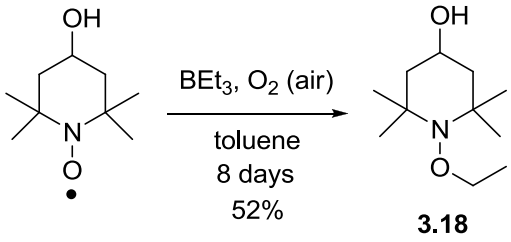
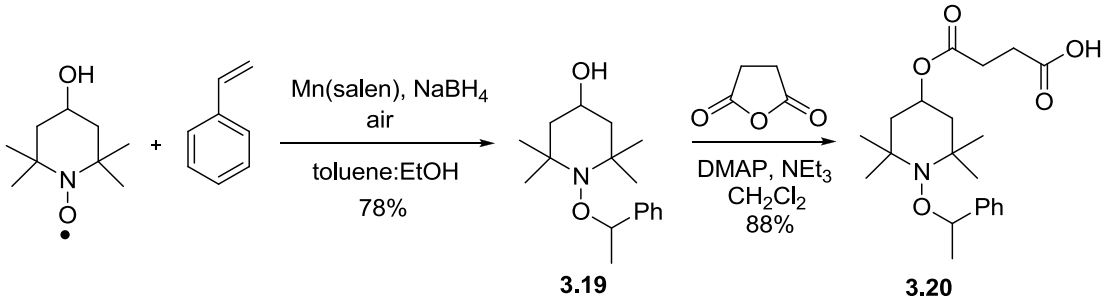


Figure 3.21 Fluorescence visualized with a 366 nm lamp of CdSe QDs (5 μM) in the presence of carboxylic acid nitroxide **3.10** (1000:1 moles of nitroxide **3.10**:QD) in toluene solution (**A**) before and (**B**) after the addition of Et_3B (open to air for 1 h; 4:1 moles of BEt_3:nitroxide **3.10**). The vial on the left contains CdSe QDs with no additive as a control.



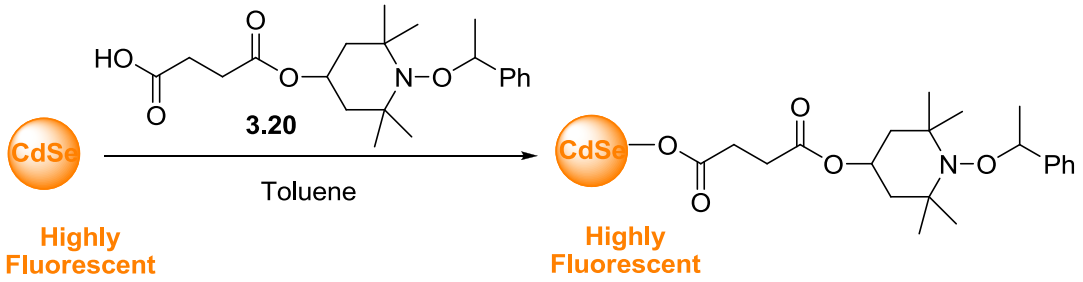
Scheme 3.10 Trapping of ethyl radicals generated from triethylborane in the presence of the air with TEMPOL provided alkoxyamine **3.18**.

To confirm that the carboxylic acid functionality was only involved in binding to the QD surface, rather than fluorescent quenching, 1-(1-phenylethoxy)-2,2,6,6-tetramethylpiperidin-4-ol **3.19** was synthesized from the reaction of TEMPOL, styrene and sodium borohydride with manganese salen catalyst and air (**Scheme 3.11**).[64] Column chromatography afforded alkoxyamine **3.19** in 78% yield. Subsequently, **3.19** was combined with succinic anhydride in the presence of triethylamine to give 4-(1-phenylethoxy-2,2,6,6-tetramethylpiperidin-4-yloxy)-4-oxobutanoic acid **3.20** in 88% yield after column chromatography. Addition of



Scheme 3.11 Synthesis of an alkoxyamine bearing a carboxylic acid **3.20**

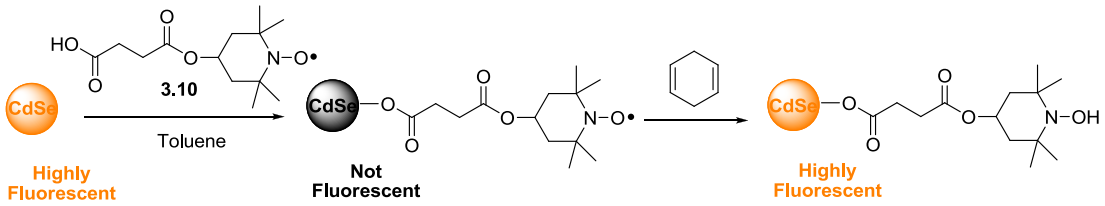
alkoxyamine **3.20** to a solution of CdSe QDs did not result in any observable quenching of CdSe QD fluorescence as seen by the naked eye (**Scheme 3.12** and **Figure 3.22**). This confirms that the carboxylic acid functionality is not responsible for quenching the QD fluorescence: the nitroxide is required.



Scheme 3.12 The fluorescence of CdSe QDs was not quenched upon addition of alkoxyamine **3.20**.

Figure 3.22 No change in fluorescence is observed for CdSe QDs (5 μM) before (left vial) and after (right vial) the addition of alkoxyamine **3.20** (1000:1 moles of alkoxyamine **3.20**:QD) in toluene solution.

An alternative method to recover the QD fluorescence is the quantitative reduction of nitroxide, as shown in **Scheme 3.13**. The reducing agent 1,4-cyclohexadiene was chosen because it is organic-soluble, and does not react with the QDs. The reductant phenyl hydrazine caused rapid decomposition of a control sample of CdSe QDs. The emission spectra in **Figure 3.23A** illustrate the recovery over time. The plot in **Figure 3.23B** (red line) shows the intensity of the emission at 594 nm as a function of the reaction time following the addition of 1,4-



Scheme 3.13 The fluorescence of the quenched CdSe QD-carboxylic acid nitroxide **3.10** complex was restored by treatment with 1,4-cyclohexadiene.

cyclohexadiene. A 30% decrease in QD fluorescence was observed upon addition of carboxylic acid nitroxide **3.10**; the reducing agent was then added, and the emission spectra were recorded. As the nitroxide underwent reduction, the fluorescence recovered, reaching its initial level (301 a.u.) after 75 min. The sample was allowed to stand for 2 h, and the fluorescence intensity remained unchanged. A control experiment was performed by addition of 1,4-cyclohexadiene to a suspension of CdSe QDs in the absence of nitroxide. The fluorescence intensity remained fairly stable over 2 h (**Figure 3.23B**, blue line), indicating that 1,4-cyclohexadiene does not significantly affect QD fluorescence. It should be noted that the control experiment (**Figure 3.23B**, blue line) was performed at higher concentration of CdSe QDs resulting in higher fluorescence intensity (373 a.u).

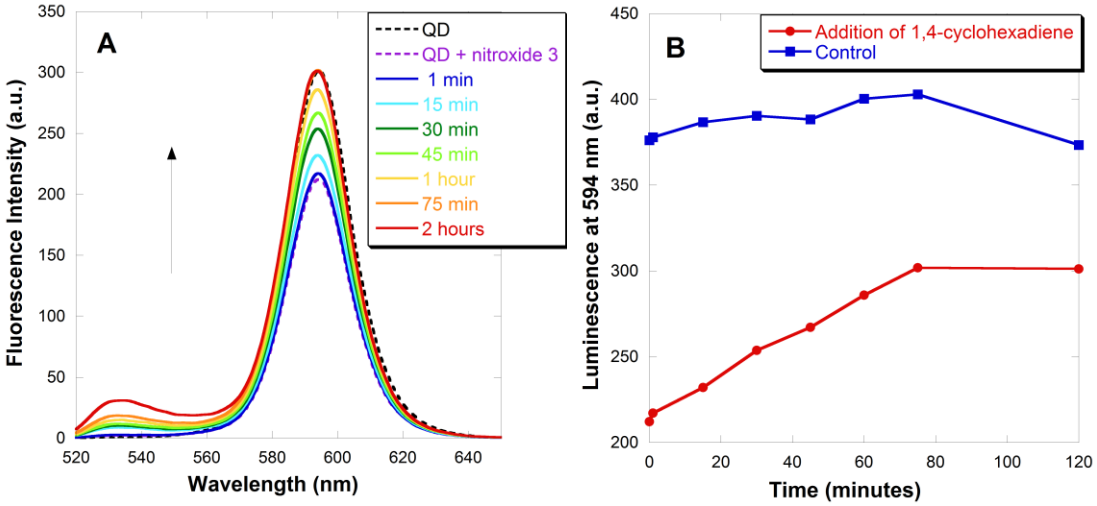


Figure 3.23 Fluorescence recovery of QD-carboxylic acid nitroxide **3.10** complex in toluene. Fluorescence emission spectra for an initial toluene suspension containing CdSe QDs (0.4 μM) and carboxylic acid nitroxide **3.10** (1:17 moles of QD:nitroxide **3.10**). At time = 0: 1,4-cyclohexadiene (100:1 moles of 1,4-cyclohexadiene:nitroxide **3.10**) was added. (**A**) Emission spectra for excitation at 390 nm, and (**B**) emission intensity at the peak maximum of 594 nm

3.6 Fluorescence Quenching Mechanisms

Quenching of tethered fluorescent organic molecules by nitroxides is known to be influenced by the excited state energy of the donor;[65, 66] however in this instance, the nitroxide absorption band (350-550 nm) is at higher energy than the band gap of the orange QDs. As a consequence, a simple energy transfer mechanism can be ruled out due to negligible spectral overlap. Absorption spectra of CdSe QDs and 4-amino-TEMPO **3.13** in toluene are shown in **Figure 3.24A-B**. Because quenching efficiency is highly dependent on distance, an electron exchange

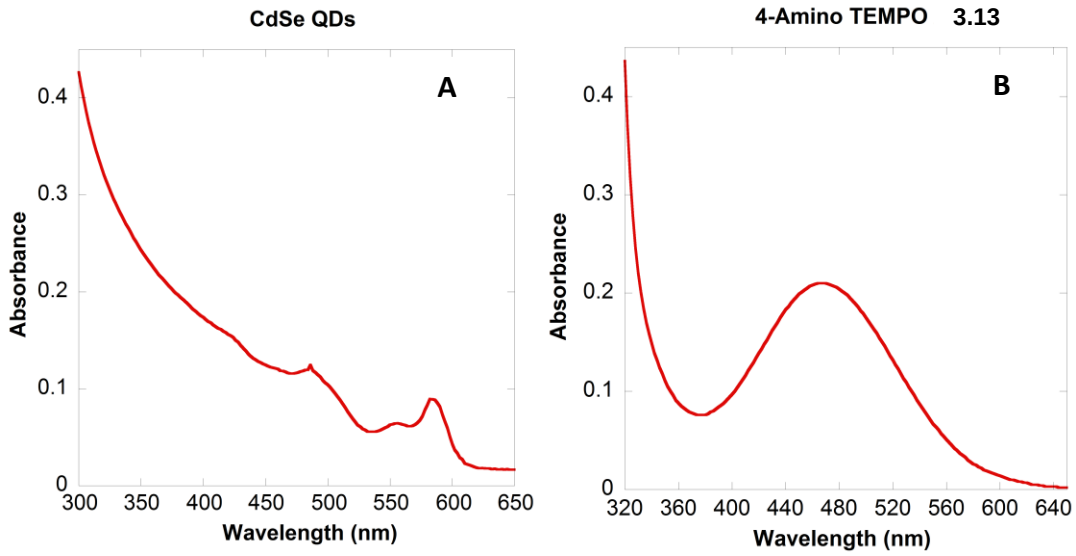


Figure 3.24 Absorption spectra of (**A**) 3.7 nm CdSe QDs (0.4 μM) (**B**) 4-amino TEMPO **3.13** (20 mM) in toluene

mechanism is likely. This mechanism requires close proximity between the electron acceptor and the excited electron in the conduction band of the electron donor. Such processes include electron spin exchange and electron transfer. Electron spin exchange involves a paramagnetic assisted spin relaxation mechanism, analogous to nitroxide induced intersystem crossing.[67, 68] Reversible electron transfer, also called an electron shuttle mechanism,[22] involves electron transfer from the conduction band of the QD to the half-filled SOMO (singly occupied molecular orbital) of the nitroxide, and back electron transfer from the nitroxide to the valence band of the QD, resulting in fluorescence quenching using the nitroxide as a shuttle for electrons and holes as illustrated in **Figure 3.25**. Examples of the electron shuttle mechanism

are the proposed mechanisms for the quenching of CdSe QDs by both *n*-butylamine[51] and by nitroxides.[22, 54]

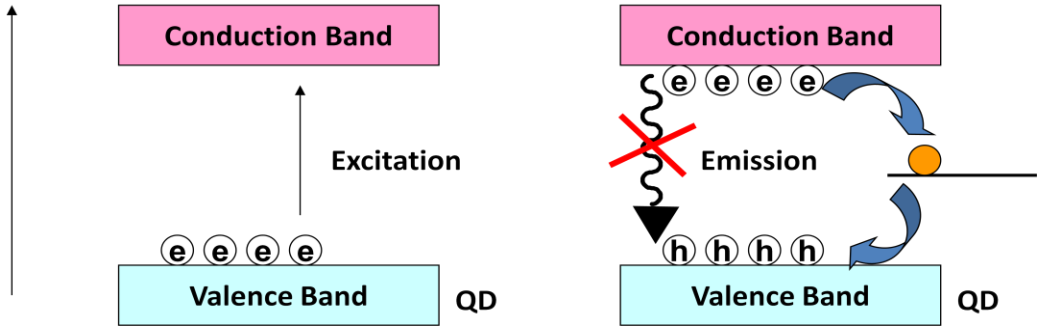
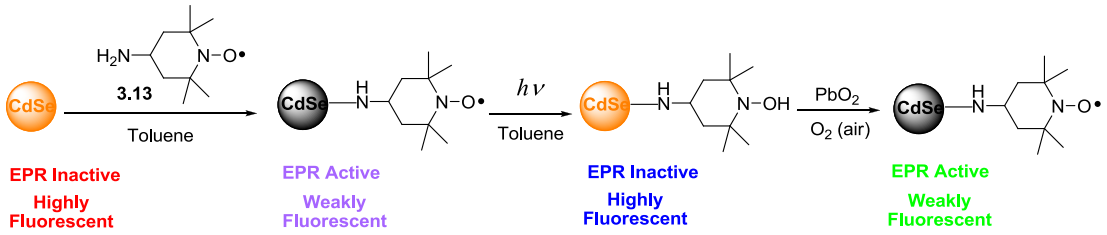


Figure 3.25 Representation of the electron shuttle mechanism of QD fluorescence quenching by nitroxides. (Note: in a semiconductor the topmost filled band is known as the valence band. The first empty band is known as the conduction band. The unoccupied state left behind in the valence band when an electron jumps to the conduction band is known as a hole.)

To probe the fluorescence quenching mechanism, photoexcitation studies were performed using a combination of EPR, fluorescence, and UV-vis spectroscopies (**Scheme 3.14**). As a control, CdSe QDs did not show a signal in the EPR spectrum (**Figure 3.26A**, red line), but strong fluorescence was observed (**Figure 3.26B**, red line, behind blue line). With the aim of photoexciting an electron in the QD from the valence band to the conduction band, with subsequent electron transfer or spin exchange with the ligated nitroxide, photoexcitation was carried out at 365 nm. The EPR signal was monitored immediately after irradiation. If electron



Scheme 3.14 Photoexcitation studies of 4-amino TEMPO **3.13** and CdSe QDs performed in toluene using a combination of EPR and fluorescence spectroscopies

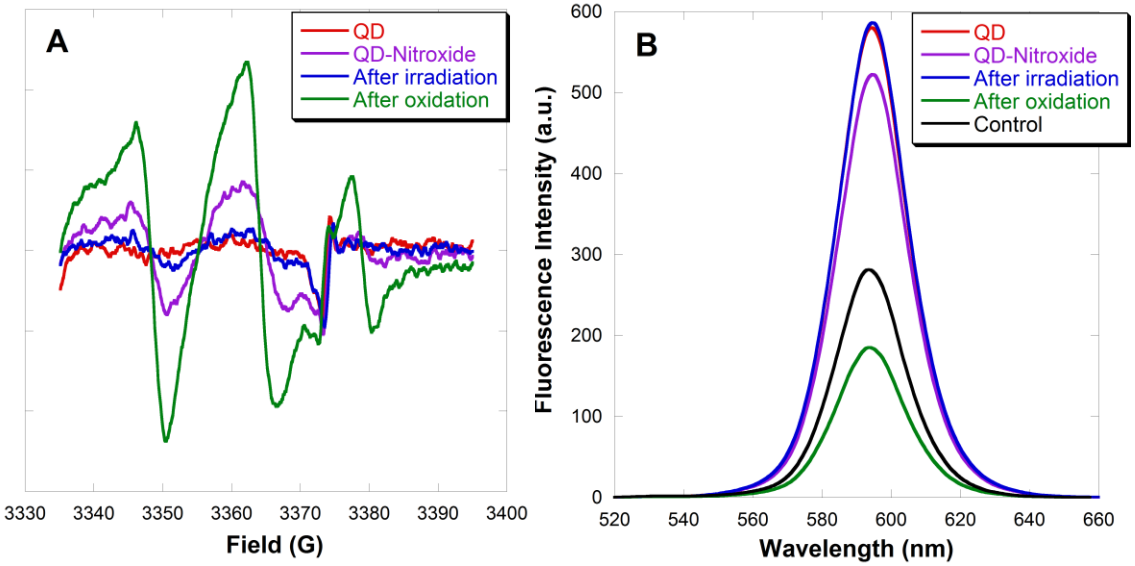


Figure 3.26 (A) EPR spectra and **(B)** fluorescence emission spectra of a toluene solution containing CdSe QDs (2 μM), followed by addition of 4-amino TEMPO **3.13** (1 μM), photoexcitation, and then chemical re-oxidation

transfer occurred and was irreversible or slow, a diminution in the EPR signal would be expected. The EPR spectrum of the QD-4-amino-TEMPO **3.13** complex in toluene solution before photoexcitation (**Figure 3.26A**, purple line) shows a broadened signal and a small peak-to-peak height at the high field peak, as expected for a nitroxide

with restricted mobility bound to the QD surface. The fluorescence intensity was diminished (**Figure 3.26B**, purple line) due to quenching by the nitroxide radical. Upon photoexcitation of the QD-nitroxide complex, a significant decay of the EPR signal and concurrent enhancement of the fluorescence intensity were observed (**Figure 3.26**, blue lines), indicating that the nitroxide had been transformed to a nonparamagnetic species. The QD concentration determined by UV-vis spectroscopy remained unchanged. The loss of the EPR signal of the photoexcited QD-nitroxide complex remained unchanged after standing for 15 h as shown in **Figure 3.27**, suggesting that the reduction process in toluene solution was irreversible.

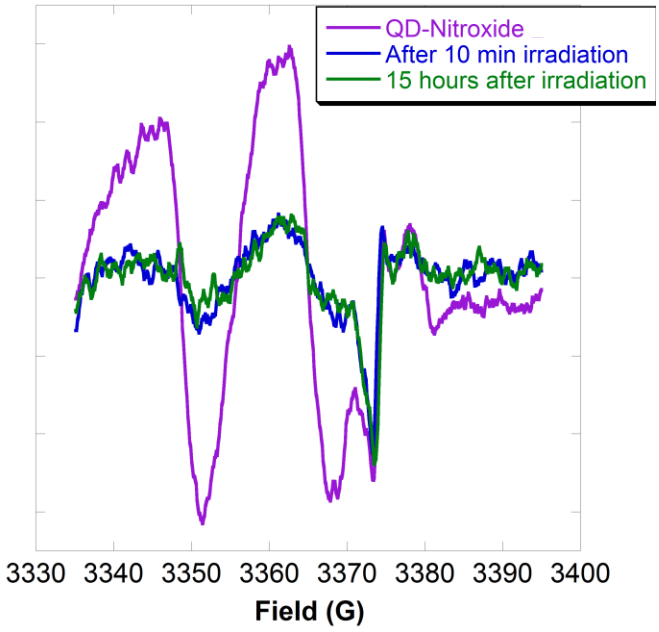


Figure 3.27 Photoexcitation studies: EPR spectra of a toluene solution containing CdSe QDs (2 μM) and 4-amino TEMPO **3.13** (1 μM); before irradiation, 10 minutes, and 15 hours after irradiation

To reform the paramagnetic nitroxide, the QD-hydroxylamine complex formed by photoexcitation was oxidized by addition of a catalytic amount of PbO_2 with exposure to air. Recovery of the EPR signal was observed (**Figure 3.26A**, green line); however, surprisingly, the fluorescence intensity (**Figure 3.26B**, green line) diminished further below the original quenching level observed with fresh nitroxide (**Figure 3.26B**, purple line). A control experiment showed that treatment with PbO_2 and air quenched the QD fluorescence (**Figure 3.26B**, black line). The recovery of the EPR signal confirms that the nitroxide was photoreduced in toluene and was then successfully chemically reoxidized.

One mechanism for this nitroxide reduction could be electron transfer from the conduction band of the QD to the nitroxide, followed by proton transfer to form the hydroxylamine. However, the reduced EPR signal could also result from photoinduced reduction of the nitroxide in toluene[69, 70] by direct photoexcitation of the nitroxide to form an excited state, followed by benzylic hydrogen abstraction from toluene. A control was carried out using free 4-amino-TEMPO **3.13** in toluene. Photoreduction to the alkoxyamine was observed in the absence of QDs as shown in **Figure 3.28**. The photoexcitation experiment on the QD-4-amino-TEMPO **3.13** complex was repeated in benzene solution, in which hydrogen abstraction cannot occur. The EPR signal of the QD-nitroxide complex in benzene before photoexcitation showed the expected broadening (**Figure 3.29A**, purple line, behind

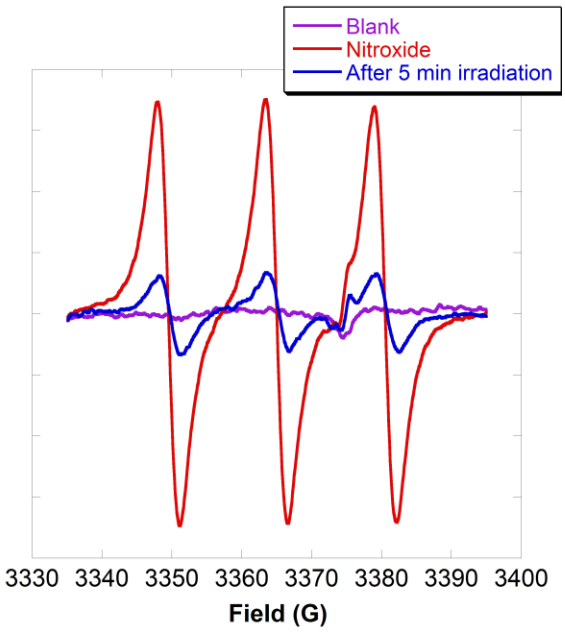


Figure 3.28 EPR spectra show of 4-amino TEMPO **3.13** (1 μM) in toluene before and after photoexcitation at 365 nm.

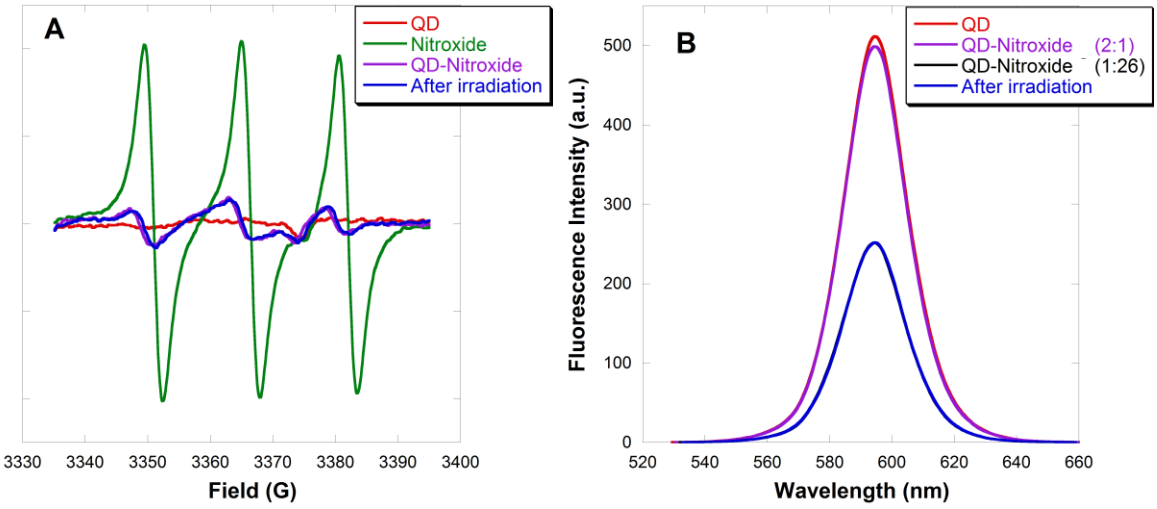


Figure 3.29 (A) EPR spectra and **(B)** fluorescence emission spectra of a benzene solution containing CdSe QDs (2 μM), followed by addition of 4-amino TEMPO **3.13** (1 μM) and then photoexcitation. (Note: an additional 25 equivalents of 4-amino TEMPO **3.13** was added in the fluorescence study.)

blue line) as compared to the free nitroxide (**Figure 3.29A**, green line). The fluorescence intensity was slightly diminished due to quenching by the nitroxide (**Figure 3.29B**, purple line); however the quenching is less effective as compared to that in toluene solution. Addition of 25 equivalents of 4-amino-TEMPO **3.13** quenched the fluorescence to a much greater extent (**Figure 3.29B**, black line, directly behind blue line). The fluorescence intensity and the EPR signal remained unchanged upon photoexcitation (**Figure 3.29**, blue lines). EPR spectra of the control experiment: 4-amino TEMPO **3.13** in benzene in the absence of CdSe QDs before and after photoexcitation is shown in **Figure 3.30**. The EPR spectrum was unchanged upon photoexcitation, confirming no phoreduction of nitroxides in benzene.

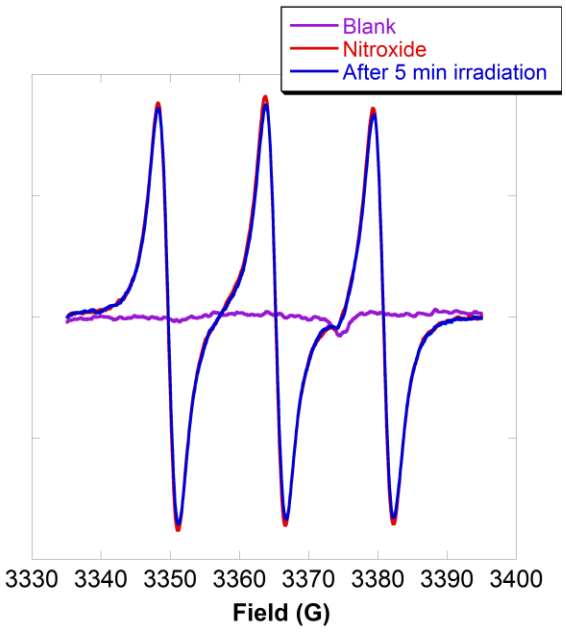


Figure 3.30 EPR spectra of 4-amino TEMPO **3.13** (1 μM) in benzene before and after photoexcitation at 365 nm

These experiments indicate that the photoreduction process in toluene solution is independent of the fluorescence quenching mechanism, but instead results from hydrogen abstraction by a photoexcited nitroxide. The quenching mechanism appears to be reversible, because no change was observed in the EPR signal upon photoexcitation. In both toluene and benzene solutions, the quenching process is due to either a fast reversible electron transfer mechanism or an electron spin exchange mechanism, as illustrated in **Figure 3.31**. These experiments cannot distinguish between these two mechanisms.[22]

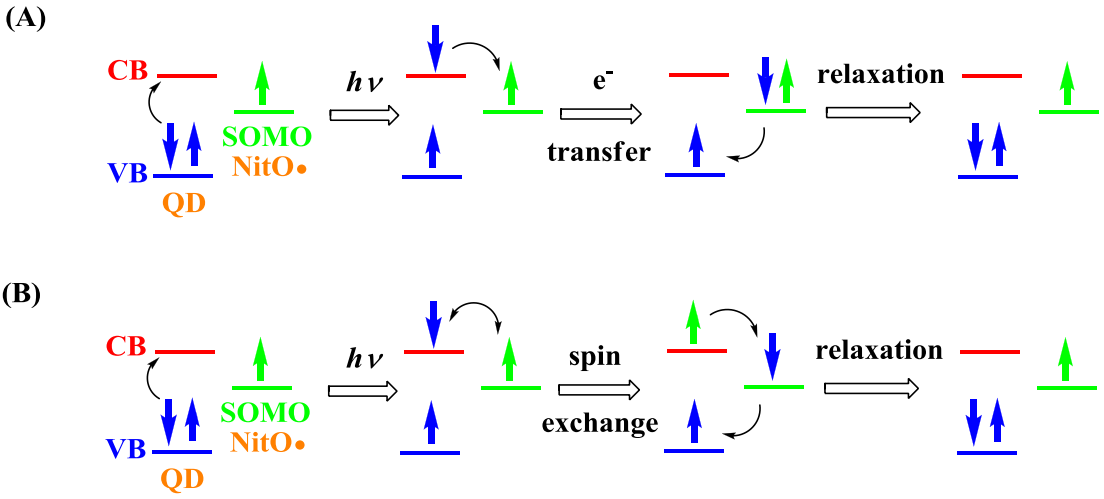


Figure 3.31 Diagrams illustrating two possible quenching mechanisms: **(A)** reversible electron transfer, and **(B)** electron spin exchange. (Note: CB = conduction band, VB = valence band, SOMO = singly occupied molecular orbital, NitO• = nitroxide radical)

3.7 Conclusion

In summary, a clear distance dependence in the fluorescence quenching by nitroxides bound to the surface of CdSe QDs has been observed. Among the four nitroxides tested, the order of quenching efficiency is 4-amino-TEMPO **3.13** > carboxylic acid nitroxide **3.10** > amino pyrrolidine nitroxide **3.17** > bisamino nitroxide **3.15**. This sequence correlates with the distance of the bound nitroxide radicals to the QD surface, except for the case of amino pyrrolidine nitroxide **3.17**, which can take part in intramolecular hydrogen bonding, dramatically diminishing its binding/quenching efficiency. The carboxylic acid nitroxide **3.10** shows tighter binding to the CdSe QDs than 4-amino-TEMPO **3.13**. Intermolecular hydrogen bonding between nitroxides strongly affects the EPR spectra of dilute solutions of the free nitroxides in toluene: the addition of chemically similar competitors breaks up the nitroxide hydrogen-bonded aggregates, resulting in a strong enhancement in the magnitude of the EPR signal. Interaction of QDs with all of these functionalized nitroxides shows bimodal quenching, as reflected in both upward and downward curved Stern-Volmer plots. The large binding constants (K_b) and static quenching constants (K_S) confirm that fluorescence quenching by nitroxides is dominated by static processes. Restoration of the QD fluorescence was demonstrated by converting the nitroxide moiety to either ethoxyamine or hydroxylamine. The EPR data in conjunction with fluorescence and UV-vis studies support photoinduced

reduction in toluene solution. Similar experiments in benzene suggest a reversible fluorescence quenching mechanism. The development of strongly binding QD-nitroxide complexes with multidentate ligands and short tethers is expected to improve the performance of profluorescent probes in the development of QD-based sensors for chemical and biological applications. The insights gained from these studies will lead to a deeper understanding of the fundamental processes that govern both fluorescence quenching of QDs by organic radicals and electron transfer or spin exchange between QDs and radicals.

3.8 References

1. Snee, P. T.; Somers, R. C.; Nair, G.; Zimmer, J. P.; Bawendi, M. G.; Nocera, D. G., *Journal of the American Chemical Society* **2006,** *128* (41), 13320-13321.

2. Tomasulo, M.; Yildiz, I.; Raymo, F. M., *Journal of Physical Chemistry B* **2006,** *110* (9), 3853-3855.

3. Mulder, W. J. M.; Koole, R.; Brandwijk, R. J.; Storm, G.; Chin, P. T. K.; Strijkers, G. J.; Donega, C. D.; Nicolay, K.; Griffioen, A. W., *Nano Letters* **2006,** *6* (1), 1-6.

4. Giepmans, B. N. G.; Adams, S. R.; Ellisman, M. H.; Tsien, R. Y., *Science* **2006,** *312* (5771), 217-224.

5. Selvan, S. T.; Patra, P. K.; Ang, C. Y.; Ying, J. Y., *Angewandte Chemie-International Edition* **2007,** *46* (14), 2448-2452.

6. Liu, W.; Howarth, M.; Greytak, A. B.; Zheng, Y.; Nocera, D. G.; Ting, A. Y.; Bawendi, M. G., *Journal of the American Chemical Society* **2008,** *130* (4), 1274-1284.

7. Schroeder, T., *Nature* **2008,** *453* (7193), 345-351.

8. Appelt, M.; Schmidt-Naake, G., *Macromolecular Materials and Engineering* **2004,** *289* (3), 245-253.

9. Williams, R. H.; Hamilton, L. A., *Journal of the American Chemical Society* **1952,** *74* (21), 5418-5420.

10. Miller, R. C.; Bradley, J. S.; Hamilton, L. A., *Journal of the American Chemical Society* **1956,** *78* (20), 5299-5303.

11. Sill, K.; Emrick, T., *Chemistry of Materials* **2004,** *16* (7), 1240-1243.

12. Clark, J. H.; Miller, J. M.; So, K. H., *Journal of the Chemical Society-Perkin Transactions 1* **1978,** (9), 941-946.

13. Delpierre, G. R.; Lamchen, M., *Journal of the Chemical Society* **1963,** (OCT), 4693-4701.

14. Liu, H. T.; Owen, J. S.; Alivisatos, A. P., *Journal of the American Chemical Society* **2007,** *129* (2), 305-312.

15. Singh, C.; Srivastav, N. C.; Puri, S. K., *Bioorganic & Medicinal Chemistry* **2004,** *12* (22), 5745-5752.

16. Tao, L.; Geng, J.; Chen, G. J.; Xu, Y. J.; Ladmiral, V.; Mantovani, G.; Haddleton, D. M., *Chemical Communications* **2007,** (33), 3441-3443.

17. Bushmakina, N. G.; Misharin, A. Y., *Synthesis-Stuttgart* **1986,** (11), 966-966.

18. Yao, S.; Schafer-Hales, K. J.; Cohanoschi, I.; Hernandez, F. E.; Belfield, K. D., *Synlett* **2006,** (12), 1863-1866.

19. Hideg, E.; Kalai, T.; Kos, P. B.; Asada, K.; Hideg, K., *Photochemistry and Photobiology* **2006,** *82* (5), 1211-1218.

20. Knauer, B. R.; Napier, J. J., *Journal of the American Chemical Society* **1976,** *98* (15), 4395-4400.

21. Laferriere, M.; Galian, R. E.; Maurel, V.; Scaiano, J. C., *Chemical Communications* **2006,** (3), 257-259.

22. Scaiano, J. C.; Laferriere, M.; Galian, R. E.; Maurel, V.; Billone, P., *Physica Status Solidi A-Applications and Materials Science* **2006,** *203* (6), 1337-1343.

23. Maurel, V.; Laferriere, M.; Billone, P.; Godin, R.; Scaiano, J. C., *Journal of Physical Chemistry B* **2006,** *110* (33), 16353-16358.

24. Chechik, V.; Wellsted, H. J.; Korte, A.; Gilbert, B. C.; Caldararu, H.; Ionita, P.; Caragheorgheopol, A., *Faraday Discussions* **2004,** *125*, 279-291.

25. Barhate, N.; Cekan, P.; Massey, A. P.; Sigurdsson, S. T., *Angewandte Chemie-International Edition* **2007,** *46* (15), 2655-2658.

26. Bahri, M. A.; Heyne, B. J.; Hans, P.; Seret, A. E.; Mouithys-Mickalad, A. A.; Hoebeke, M. D., *Biophysical Chemistry* **2005,** *114* (1), 53-61.

27. Hafner, A.; Hrast, M.; Pecar, S.; Mravljak, J., *Tetrahedron Letters* **2009,** *50* (5), 564-566.

28. Sharma, S. N.; Pillai, Z. S.; Kamat, P. V., *Journal of Physical Chemistry B* **2003,** *107* (37), 10088-10093.

29. Jones, M.; Nedeljkovic, J.; Ellingson, R. J.; Nozik, A. J.; Rumbles, G., *Journal of Physical Chemistry B* **2003,** *107* (41), 11346-11352.

30. Kalyuzhny, G.; Murray, R. W., *Journal of Physical Chemistry B* **2005,** *109* (15), 7012-7021.

31. Roberti, T. W.; Cherepy, N. J.; Zhang, J. Z., *Journal of Chemical Physics* **1998,** *108* (5), 2143-2151.

32. Zotti, G.; Vercelli, B.; Berlin, A.; Chin, P. T. K.; Giovanella, U., *Chemistry of Materials* **2009,** *21* (11), 2258-2271.

33. Marshall, J. H., *Journal of Chemical Physics* **1971,** *54* (6), 2762-2763.

34. Veloso, D. P.; Rassat, A., *Journal of Chemical Research-S* **1979,** (5), 168-169.

35. Kooser, R. G., *Macromolecules* **1987,** *20* (2), 435-436.

36. Rozantsev, E. G., *Free Nitroxyl Radicals*. Plenum Press: New York, 1970.

37. Tkacheva, O. P.; Martin, V. V.; Volodarskii, L. B.; Buchachenko, A. L., *Bulletin of the Academy of Sciences of the Ussr Division of Chemical Science* **1981,** *30* (5), 913-915.

38. Janzen, E. G.; Lopp, I. G., *Journal of Magnetic Resonance* **1972,** *7* (1), 107-110.

39. Kotake, Y.; Kuwata, K., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **1982,** *60* (12), 1610-1613.

40. Matsushita, M. M.; Izuoka, A.; Sugawara, T.; Kobayashi, T.; Wada, N.; Takeda, N.; Ishikawa, M., *Journal of the American Chemical Society* **1997,** *119* (19), 4369-4379.

41. Marque, S.; Fischer, H.; Baier, E.; Studer, A., *Journal of Organic Chemistry* **2001,** *66* (4), 1146-1156.

42. Ahrens, B.; Davidson, M. G.; Forsyth, V. T.; Mahon, M. F.; Johnson, A. L.; Mason, S. A.; Price, R. D.; Raithby, P. R., *Journal of the American Chemical Society* **2001,** *123* (37), 9164-9165.

43. Russ, J. L.; Gu, J.; Tsai, K. H.; Glass, T.; Duchamp, J. C.; Dorn, H. C., *Journal of the American Chemical Society* **2007,** *129* (22), 7018-7027.

44. Rajadurai, C.; Enkelmann, V.; Zoppellaro, G.; Baumgarten, M., *Journal of Physical Chemistry B* **2007,** *111* (17), 4327-4334.

45. Paola, F.; Marco, L.; Pamela, P.; Gian Franco, P., *ChemPhysChem* **2002,** *3* (9), 789-793.

46. Kalai, T.; Hideg, E.; Vass, I.; Hideg, K., *Free Radical Biology and Medicine* **1998,** *24* (4), 649-652.

47. Lakowicz, J. R., *Principles of Fluorescence Spectroscopy*. 3rd ed.; Springer Science/Business Media: Singapore, 2006.

48. von Smoluchowski, M., *Zeitschrift Fur Physikalische Chemie-Stochiometrie Und Verwandtschaftslehre* **1917,** *92* (2), 129-168.

49. Boaz, H.; Rollefson, G. K., *Journal of the American Chemical Society* **1950,** *72* (8), 3435-3443.

50. Zelent, B.; Kusba, J.; Gryczynski, I.; Johnson, M. L.; Lakowicz, J. R., *Journal of Physical Chemistry* **1996,** *100* (47), 18592-18602.

51. Landes, C.; Burda, C.; Braun, M.; El-Sayed, M. A., *Journal of Physical Chemistry B* **2001,** *105* (15), 2981-2986.

52. Landes, C. F.; Braun, M.; El-Sayed, M. A., *Journal of Physical Chemistry B* **2001,** *105* (43), 10554-10558.

53. Cordes, D. B.; Gamsey, S.; Singaram, B., *Angewandte Chemie-International Edition* **2006,** *45* (23), 3829-3832.

54. Chen, W. B.; Wang, X.; Tu, X. J.; Pei, D. J.; Zhao, Y.; Guo, X. Q., *Small* **2008,** *4* (6), 759-764.

55. Alivisatos, A. P., *Science* **1996,** *271* (5251), 933-937.

56. Alivisatos, A. P., *Journal of Physical Chemistry* **1996,** *100* (31), 13226-13239.

57. Lozinsky, E.; Martin, V. V.; Berezina, T. A.; Shames, A. I.; Weis, A. L.; Likhtenshtein, G. I., *Journal of Biochemical and Biophysical Methods* **1999,** *38* (1), 29-42.

58. Tang, Y. L.; He, F.; Yu, M. H.; Wang, S.; Li, Y. L.; Zhu, D. B., *Chemistry of Materials* **2006,** *18* (16), 3605-3610.

59. Aliaga, C.; Juarez-Ruiz, J. M.; Scaiano, J. C.; Aspee, A., *Organic Letters* **2008,** *10* (11), 2147-2150.

60. Petzold, H.; Sadler, P. J., *Chemical Communications* **2008,** (37), 4413-4415.

61. Lebedev, A. V.; Levitskaya, E. L.; Tikhonova, E. V.; Ivanova, M. V., *Biochemistry-Moscow* **2001,** *66* (8), 885-893.

62. Keddie, D. J.; Johnson, T. E.; Arnold, D. P.; Bottle, S. E., *Organic & Biomolecular Chemistry* **2005,** *3* (14), 2593-2598.

63. Liu, J. T.; Jang, Y. J.; Shih, Y. K.; Hu, S. R.; Chu, C. M.; Yao, C. F., *Journal of Organic Chemistry* **2001,** *66* (18), 6021-6028.

64. Choudary, B. M.; Kantam, M. L.; Bharathi, B.; Reddy, C. R. V., *Journal of Molecular Catalysis A-Chemical* **2001,** *168* (1-2), 69-73.

65. Gijzeman, O. L.; Kaufman, F.; Porter, G., *Journal of the Chemical Society-Faraday Transactions I* **1973,** *69* (5), 727-737.

66. Watkins, A. R., *Chemical Physics Letters* **1974,** *29* (4), 526-528.

67. Scaiano, J. C., *Tetrahedron* **1982,** *38* (6), 819-824.

68. Giacobbe, E. M.; Mi, Q. X.; Colvin, M. T.; Cohen, B.; Ramanan, C.; Scott, A. M.; Yeganeh, S.; Marks, T. J.; Ratner, M. A.; Wasielewski, M. R., *Journal of the American Chemical Society* **2009,** *131* (10), 3700-3712.

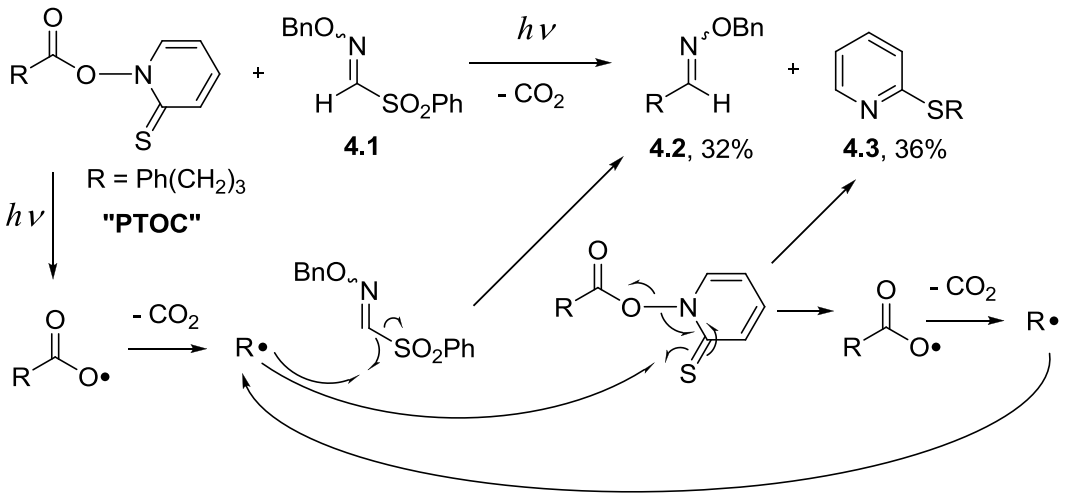
69. Keana, J. F. W.; Dinerste.Rj; Baitis, F., *Journal of Organic Chemistry* **1971,** *36* (1), 209-211.

70. Johnston, L. J.; Tencer, M.; Scaiano, J. C., *Journal of Organic Chemistry* **1986,** *51* (14), 2806-2808.

Chapter 4: Development of a Photocleavable Profluorescent Nitroxide and a Profluorescent Nitroxide as a Probe for Reducing Agents

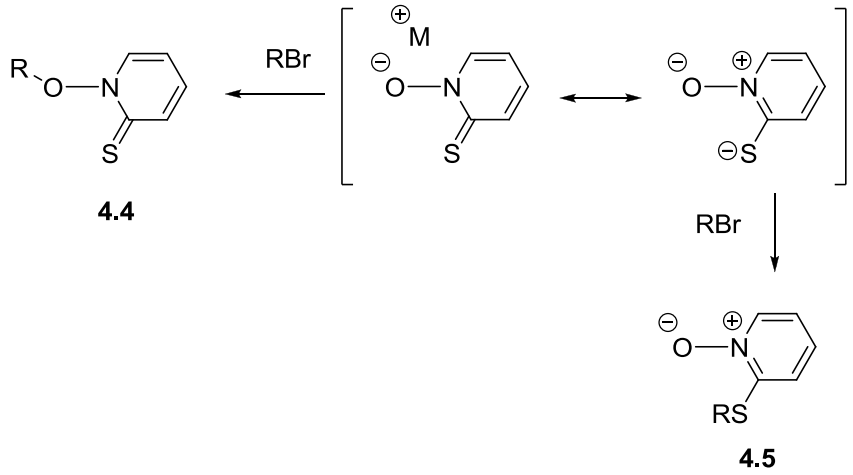
4.1 Background on Photocleavable Thiohydroxamates

Thiocarbonyl-containing compounds such as xanthates and thiohydroxamates have been used as radical precursors in radical chemistry.[1] Since first introduced by Barton, thiohydroxamates have attracted a great deal of attention as useful precursors of alkyl,[2] aminyl,[3] and alkoxycarbonyloxy[4] radicals. Barton demonstrated that pyridine-2-thione-*N*-oxycarbonyl (PTOC) esters can be used not only for the introduction of synthetically useful functional groups such as halide[5] and nitrile,[6] but also to accomplish a wide range of reactions forming C-H, C-C, and C-X bonds (X = heteroatom such as O, N, S, Se, P, etc.).[7] However, the use of PTOC is somewhat limited because they are very reactive. Highly reactive trapping agents are required to prevent the competitive addition of the alkyl radical to the thiocarbonyl group of PTOC to form pyridyl sulfides. As shown in **Scheme 4.1**, decarboxylative acylation of PTOC using phenylsulfonyl oxime ether **4.1** as an acylating trapping agent gave a mixture of the desired oxime ether **4.2** and the undesired pyridyl sulfide **4.3** in a roughly equal ratio.[8] In addition, the generation of alkoxy radicals via PTOC esters is obstructed due to the difficulty of the preparation



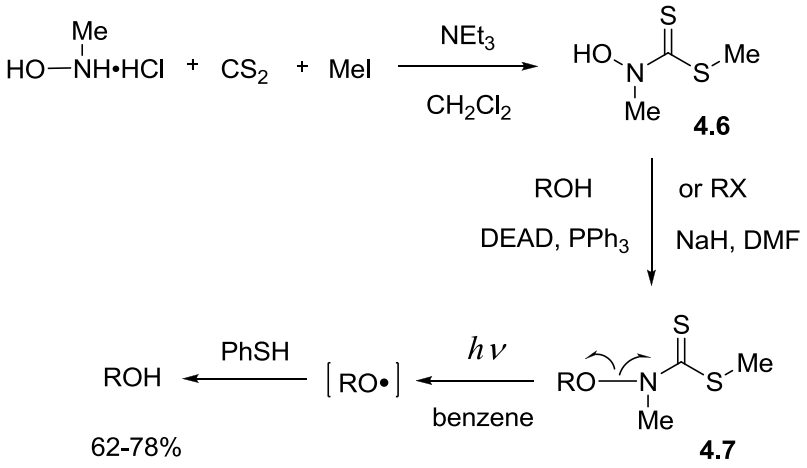
Scheme 4.1 Kim's decarboxylative acylation of PTOC esters

of the precursor **4.4**, because alkylations of the thiohydramic salt occur at sulfur rather than at oxygen[9] to form pyridyl sulfide **4.5**, **Scheme 4.2**. Further studies on the generation of alkoxy radicals using similar types of thiohydroxamic esters have not been widely investigated.[10]



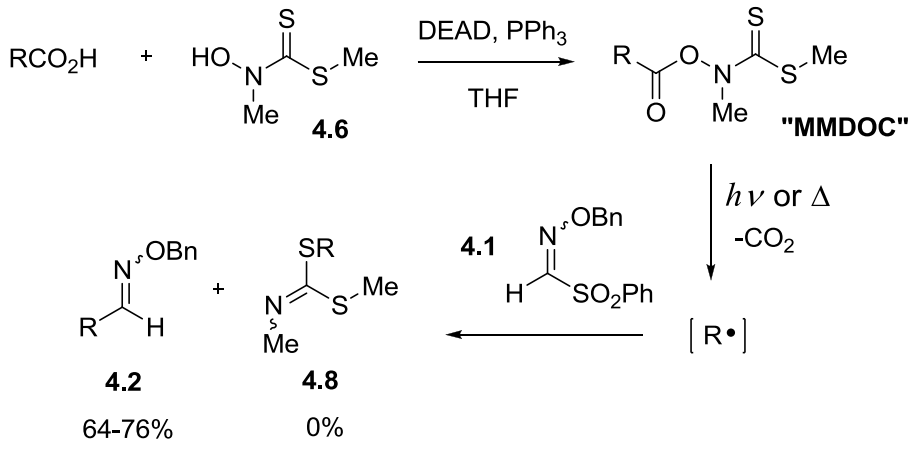
Scheme 4.2 Preparation of thiohydroxamic ester **4.4** and *S*-alkylated side product **4.5**

The key solution of this problem is to reduce the rate of alkyl radical addition onto the thiocarbonyl group to inhibit the formation of side product **4.3**. This problem was solved to some extent by Kim *et al*.,[11] using the more stable, and thus less reactive *N*-alkoxydithiocarbamates **4.7**. *N*-Methylhydroxydithiocarbamate **4.6** was readily prepared in quantitative yield by treatment of *N*-methylhydroxylamine hydrochloride with carbon disulfide, methyl iodide, and triethylamine (**Scheme 4.3**). The preparation of **4.7** was carried out using alkyl halides or alcohols as substrates. Treatment of the sodium salt of **4.6** with alkyl bromides in DMF gave **4.7**, which are stable on silica gel and upon heating. Alternatively, **4.7** were prepared by treatment of alcohols with **4.6**, diethyl azodicarboxylate (DEAD), and triphenylphosphine (PPh_3) in tetrahydrofuran using the Mitsunobu method. Both methods were equally effective and provided **4.7** in high yields. A benzene solution of **4.7** was then irradiated at 300 nm for 8 hours to generate alkoxy radicals, which were readily reduced by PhSH to form alcohols in good isolated yields. Thermal radical fragmentation with initiator gave better yields than the photochemical conditions.

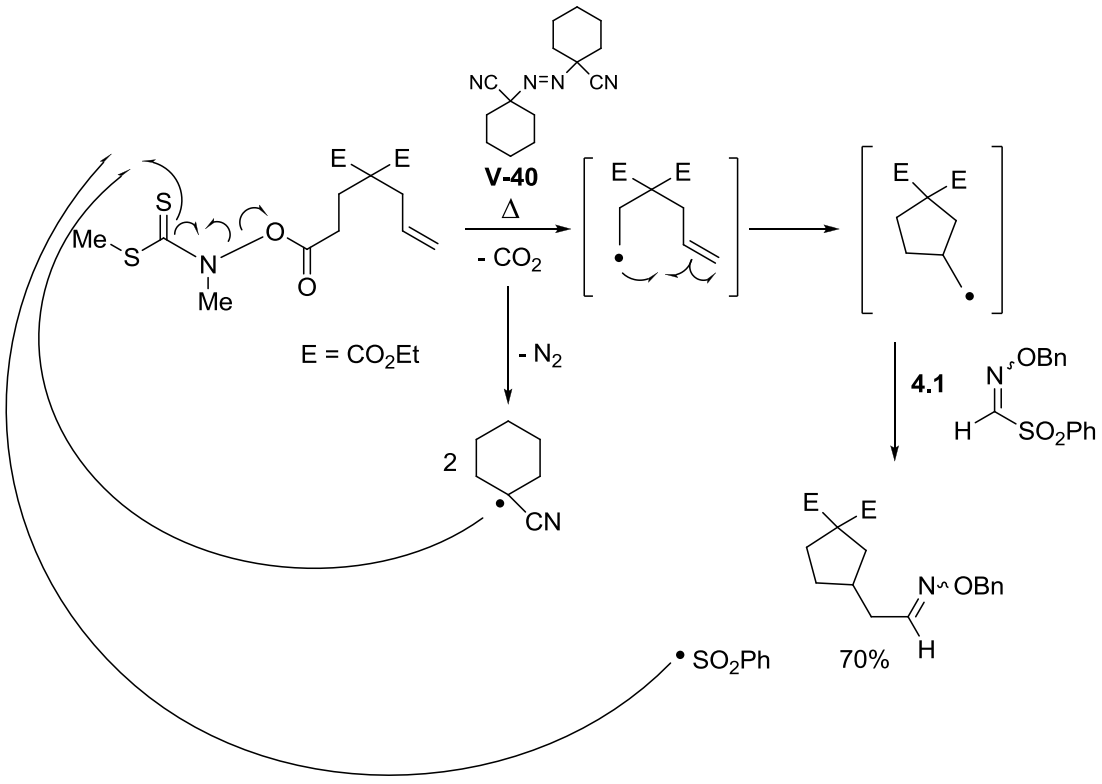


Scheme 4.3 Kim's synthesis of *N*-methylhydroxydithiocarbamate **4.6**, formation of the corresponding alkoxyamine **4.7**, and photolysis to form alkoxy radical which abstracts hydrogen from thiophenol

Later, *N*,*S*-dimethyldithiocarbamoyl-*N*-oxycarbonyl (MMDOC) esters were prepared by reaction of carboxylic acids and dithiocarbamate **4.6** (**Scheme 4.4**) in a similar fashion.[12] This decarboxylative approach to alkyl radical formation, followed by acylation could be performed thermally or photochemically. Irradiation at 300 nm of a benzene solution of MMDOC ester with phenylsulfonyl oxime ether **4.1** as an acyl trapping agent for 9 hours afforded oxime ethers **4.2** in good yields, without the formation of rearrangement product **4.8**. Primary, secondary and sterically hindered tertiary aliphatic carboxylic acids worked well. Again, thermal conditions gave higher yields than photochemical conditions. A nice demonstration of this method is a sequential decarboxylative cyclization and acylation using 1,1'-azobis(cyclohexane-1-carbonitrile) (V-40) as a thermal radical initiator (**Scheme 4.5**).

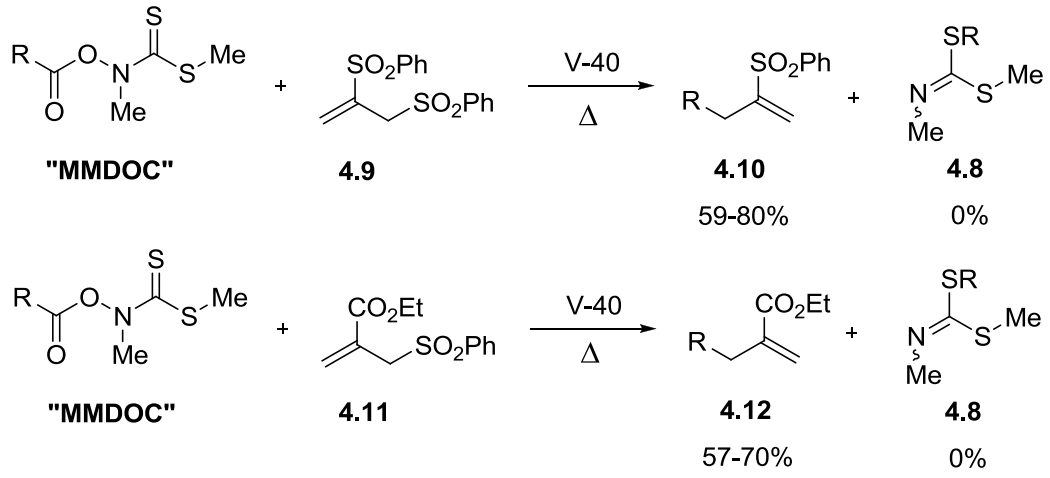


Scheme 4.4 Kim's synthesis of MMDOC esters and decarboxylative acylation to form oxime ethers **4.2**



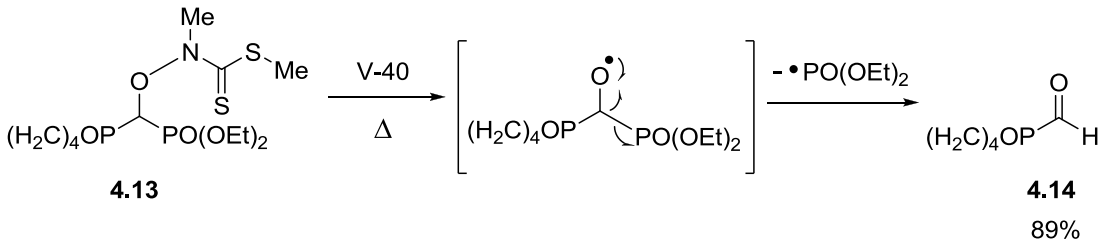
Scheme 4.5 Kim's sequential cyclization and decarboxylative acylation approach

Decarboxylative allylation was also carried out with MMDOC **esters** and allyl sulfones **4.9** or **4.11** as the trapping agent, using V-40 as the initiator in chlorobenzene at 110 °C for 10 hours (**Scheme 4.6**).[13] The allylation products **4.10** and **4.12** were isolated in good yields without giving undesired by-product **4.8**. The alkyl radical preferentially attacks the allyl sulfone rather than adding to the MMDOC ester. However, reaction of MMDOC ester with allyl sulfone **4.9** under photolytic condition (UV lamp, 300 nm) provided a mixture of **4.10** and **4.8**. The success of the decarboxylative allylation approach using **4.9** under thermal conditions is due to the thermal stability of MMDOC esters.



Scheme 4.6 Decarboxylative allylation of MMDOC esters with allyl sulfones **4.9** or **4.11** under thermal conditions

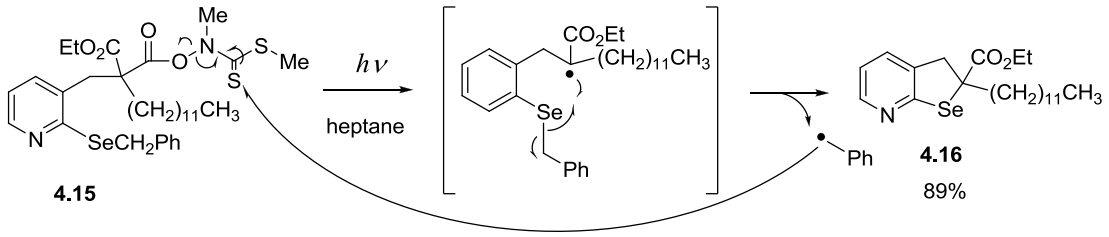
β-elimination of the diethyl phosphonate group from an alkoxy radical using a thiohydroxamate ester **4.13** was investigated.[14] As shown in **Scheme 4.7**, when **4.13** was treated with V-40 as initiator in chlorobenzene for 3 hours, providing aldehyde **4.14** in 89% yield. The β-elimination is energetically favorable because of the formation of a strong carbonyl C=O bond along with cleavage of a relatively weak carbon–phosphorous bond.



4.13 **4.14** 89%

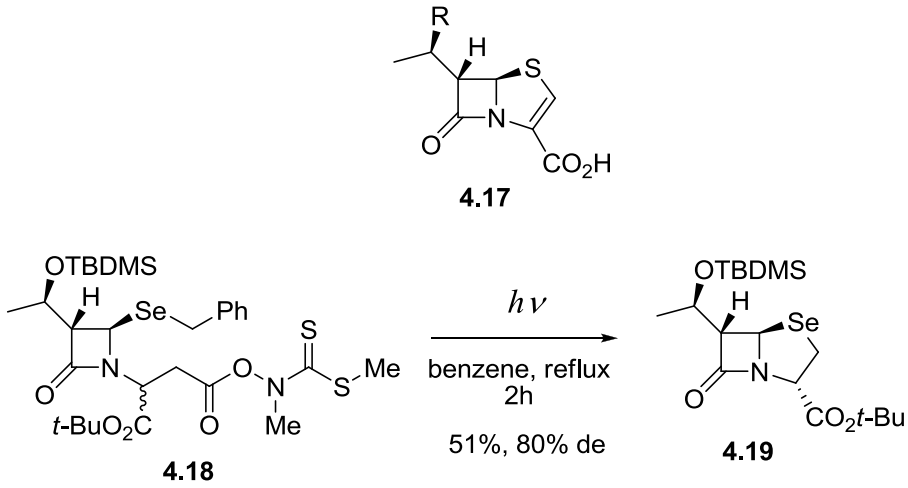
Scheme 4.7 Kim's β-elimination of the diethyl phosphonate group using thiohydroxamate ester **4.13** to generate aldehyde **4.14**

Schiesser *et al*.[15] utilized Kim's MMDOC ester to prepare an analogue of ebselen: a potent antioxidant that acts as a glutathione peroxidase mimic, and related antiinflammatory compounds with improved water solubility and therefore oral bioavailability properties. Photolysis of thiohydroxamate **4.15** in heptane formed a stabilized alkyl radical that underwent intramolecular homolytic substitution to afford the target pyridine-fused selenium-containing antioxidant **4.16** in 89% yield (**Scheme 4.8**).



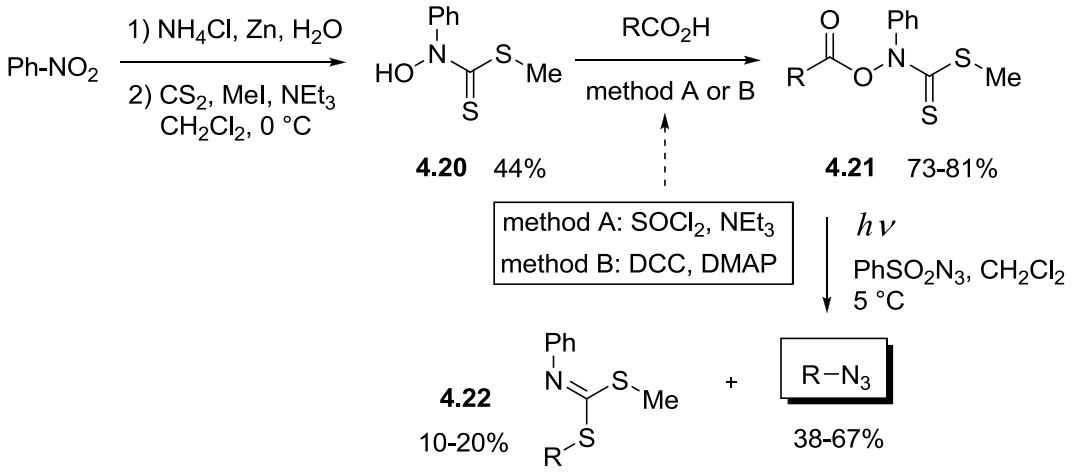
Scheme 4.8 Schiesser's photolysis of thiohydroxamate **4.15** to form ebselen analogue **4.16**

The same research group expanded this chemistry to include the synthesis of a selenium analogue of penem and cephem β-lactam antibiotics (*e.g.* **4.17**).[16] Photolysis of thiohydroxamate **4.18** provided selenapenam **4.19** in 51% yield (based on the carboxylic acid starting material) in 80% diastereomeric excess (**Scheme 4.9**).



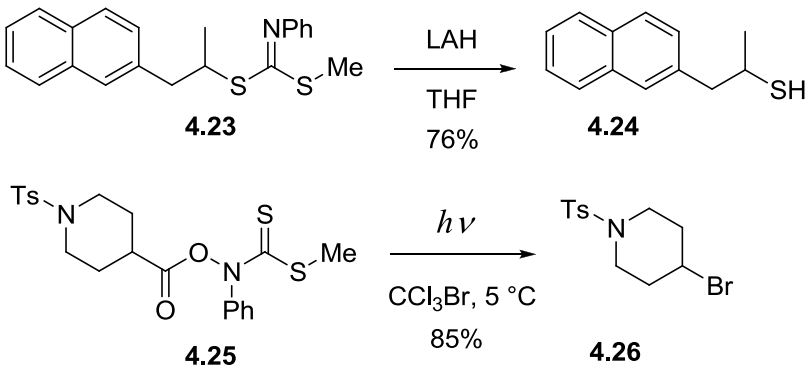
Scheme 4.9 Schiesser's photolysis of thiohydroxamate **4.18** to form selenapenam **4.19**

Nyfeler and Renaud[17] investigated decarboxylative radical azidation using MMDOC esters; however the high reaction temperatures only gave the desired product in moderate yield due to decomposition of benzenesulfonyl azide starting material. Moreover, irradiation at 300 nm with a low-pressure mercury lamp is incompatible with sulfonyl azides. As a consequence, the *N*-Me group of MMDOC ester was replaced by an *N*-Ph group, and thus enabled photochemical initiation using a standard sunlamp. This modification resulted in only a moderate increase in the reactivity of the thiohydroxamic ester as a radical trap, with a minimal decrease in the thermal stability compared to MMDOC esters. *N*-Hydroxy-*S*-methyl-*N*-phenyldithiocarbamate **4.20** was prepared from nitrobenzene in two steps (**Scheme 4.10**). The MPDOC (*S*-methyl-*N*-phenyl-1,3-dithiocarbamoyloxycarbonyl) esters **4.21** were formed from the corresponding carboxylic acids and dithiocarbamate **4.20** in good yields, and protection against daylight was not required. MPDOC esters **4.21** irradiated with a 300 W sunlamp in the presence of benzenesulfonyl azide underwent decarboxylative azidation to give the corresponding azides as major products. The only side product observed in these reactions is the rearranged product **4.22**.



Scheme 4.10 Nyfeler and Renaud's synthesis of MPDOC esters **4.21** and decarboxylative radical azidation

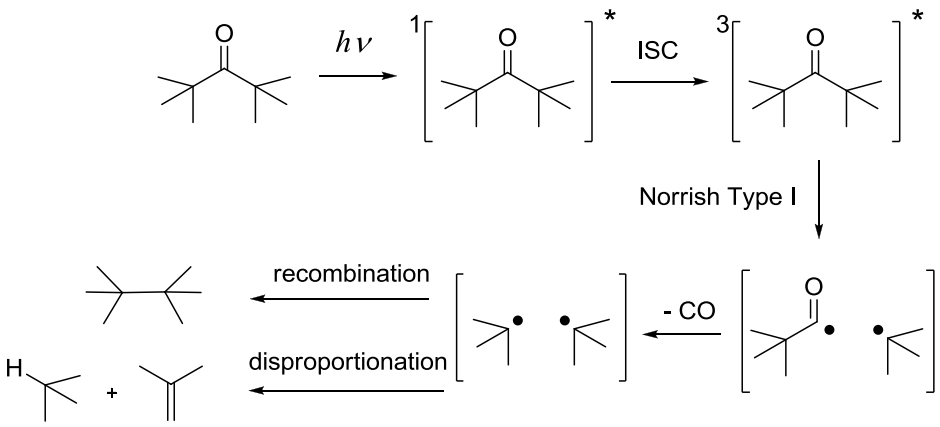
Renaud also demonstrated that the decarboxylative rearrangement of MPDOC esters is a practical method for the transformation of carboxylic acids into thiols by reductive treatment of rearranged product **4.23** with lithium aluminum hydride (LAH) to afford **4.24** in 76% yield (**Scheme 4.11**). In addition, treatment of ester **4.25** with CCl_3Br afforded the brominated product **4.26** in 85% yield (**Scheme 4.11**). However, MPDOC esters of α-amino and α-alkoxy acids were too reactive to perform decarboxylative azidation. These reactions were achieved by using the less reactive Kim's MMDOC esters in the presence of an initiator under thermal conditions. Overall, the order of increasing reactivity of thiocarbamates as a radical trap is: MMDOC, MPDOC and PTOC esters.



Scheme 4.11 Synthesis of thiol **4.24** and brominated product **4.26**

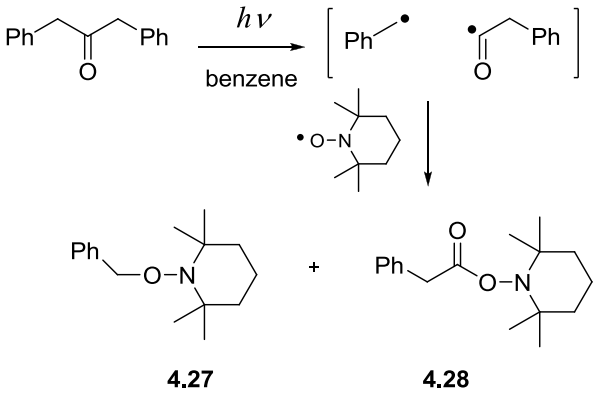
4.2 Background on Norrish Type I Photocleavage Reactions

Photochemistry of carbonyl compounds has been extensively investigated. These substrates are particularly attractive since their absorptions are very accessible: such compounds can be irradiated even with sunlight. The Norrish type I reaction denotes homolytic cleavage of a carbon-carbon bond adjacent to a carbonyl group (α-bond) initiated by an *n*-π* excitation, often followed by decarbonylation of the acyl radical intermediate (**Scheme 4.12**). The bond cleavage in the *n*-π* excited state only takes place if the excitation energy is converted into vibrational energy localized in the bond undergoing fission. This reaction can be accompanied by competing processes, such as the Norrish type II reaction or photoreduction. Typically the Norrish type I reaction of acyclic and cyclic ketones in solution results in decarbonylation, followed by recombination, and disproportionation (**Scheme 4.12**).[18]



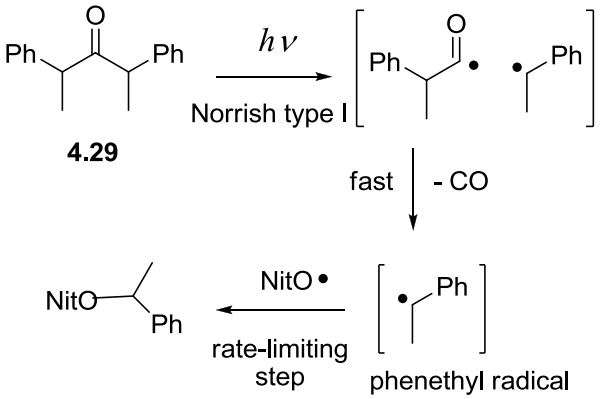
Scheme 4.12 Norrish type I cleavage, followed by decarbonylation, and then recombination or disproportionation

A two-step rather than a concerted mechanism for Norrish type I photocleavage was proved by photolysis of dibenzylketone in benzene solution. The resulting phenylacetyl and benzyl radical species were trapped by 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) to yield two products: **4.27** and **4.28** in a 3:2 ratio as shown in **Scheme 4.13**.[19]



Scheme 4.13 Norrish type I cleavage of dibenzylketone, followed by trapping the generated radicals with TEMPO

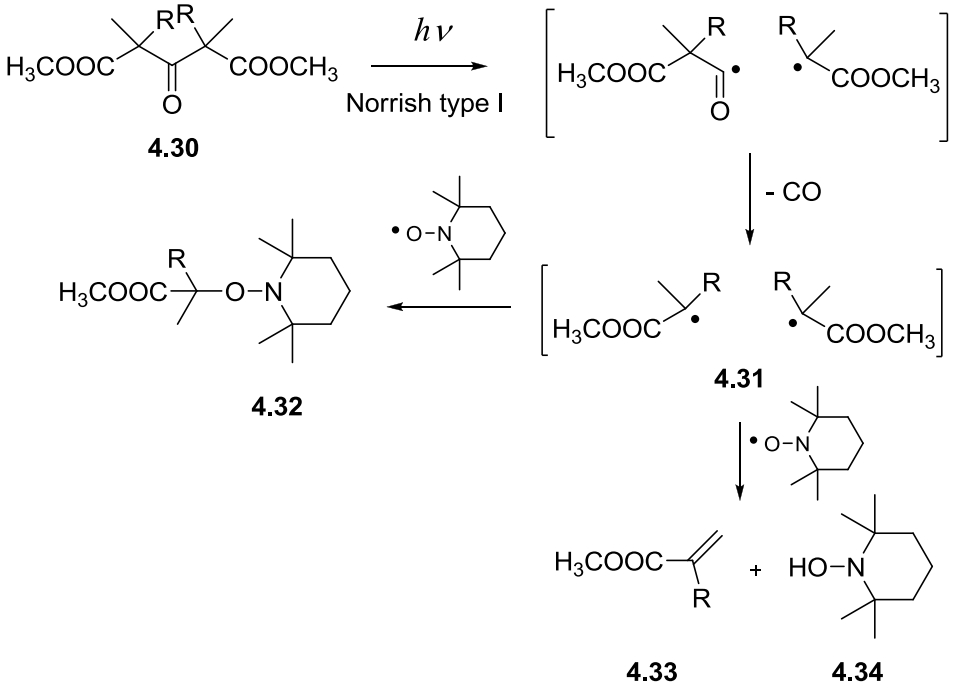
Scaiano *et al*.[20] have used structurally different nitroxides to analyze the rate constants for the trapping of carbon-centered radicals generated using the Norrish type I cleavage in order to determine initiators suitable for living free radical polymerization. Upon photolysis of **4.29**, α-cleavage occurs, giving a 1-phenylethyl radical and an acyl radical that rapidly decarbonylates to give another 1-phenylethyl radical (**Scheme 4.14**). 1-Phenylethyl radical was chosen since it is structurally similar to the propagating radical in the polymerization of styrene. The technique of laser flash photolysis was used because the rates measured are very accurate, as the radical is generated within the time of the laser pulse (~10 ns), and the trapping reaction becomes the rate-limiting step.



Scheme 4.14 Norrish type I cleavage of ketone **4.29** to form two phenethyl radicals which are trapped by nitroxides

To obtain more information on the coupling reaction between ester-substituted radicals and TEMPO, the radical **4.31** was generated by laser pulse

photolysis of ketone precursor **4.30** in the presence of TEMPO to form alkoxyamine **4.32** (**Scheme 4.15**).[21] Apparent hydrogen abstraction by TEMPO from **4.31** was a minor pathway; since the products **4.33** and **4.34** were formed in less than 3%.

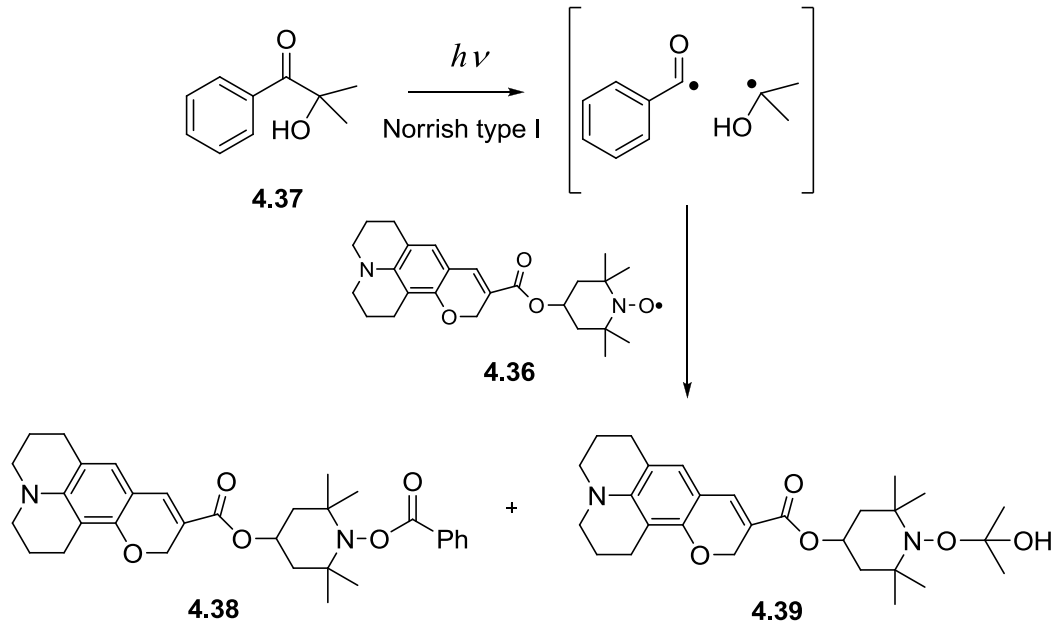


Scheme 4.15 Norrish type I cleavage of ketone **4.30** to generate ester-substituted radicals **4.31**, followed by reaction with TEMPO

4.3 Profluorescent Nitroxides as Detectors of Norrish Type I Cleavage

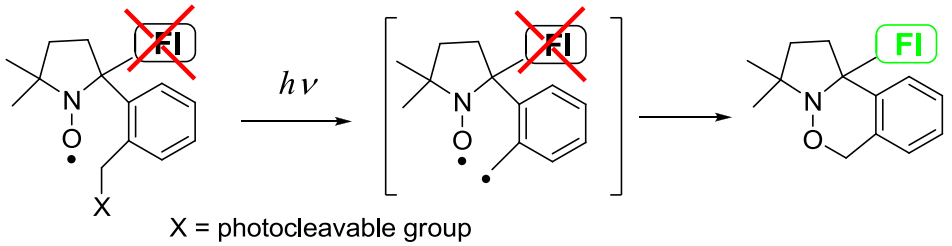
Nitroxide free radicals are effective quenchers of the fluorescence of pendent organic fluorophores; these are often referred to as "profluorescent nitroxides" (see Chapter 2). These spin-labeled pro-fluorophores can be "switched-

on" when the paramagnetic nitroxide is converted to a diamagnetic species. Scaiano *et al*.[22] demonstrated carbon radical trapping within a solid polymer matrix by preparing thin poly(methyl methacrylate) films doped with profluorescent nitroxide **4.36** and radical photo-initiator **4.37**. The film was exposed to light to photo-induce the formation of radicals, which were trapped by profluorescent nitroxide **4.36** to provide a fluorescent polymer film containing alkoxyamines **4.38** and **4.39** (**Scheme 4.16**). In another study, benzyl radicals derived from Norrish type I cleavage of dibenzyl ketone were monitored in a NaY zeolite using a quinoline containing-profluorescent nitroxide. The steady-state and time-resolved fluorescence showed a strong interaction of the profluorescent nitroxide within the zeolite cavities.[23]



Scheme 4.16 Norrish type I cleavage of photoinitiator **4.37**, followed by trapping with profluorescent nitroxide **4.36** to form fluorescent alkoxyamines **4.38** and **4.39**

The Braslau research group utilizes profluorescent nitroxides in developing novel sensors. This chapter presents two synthetic approaches to develop nitroxide radicals bearing side groups that are photolytically cleavable: upon irradiation the nitroxide will trap the nascent radical to form a 6-membered ring. When a fluorescent tag is appended to these nitroxides, the fluorescence which is originally quenched by the nitroxide will be restored upon photoexcitation following by bond cleavage (**Scheme 4.17**). These photocleavable profluorescent nitroxides will be useful for site-specific labeling of complex biological systems or materials by localized laser excitation.



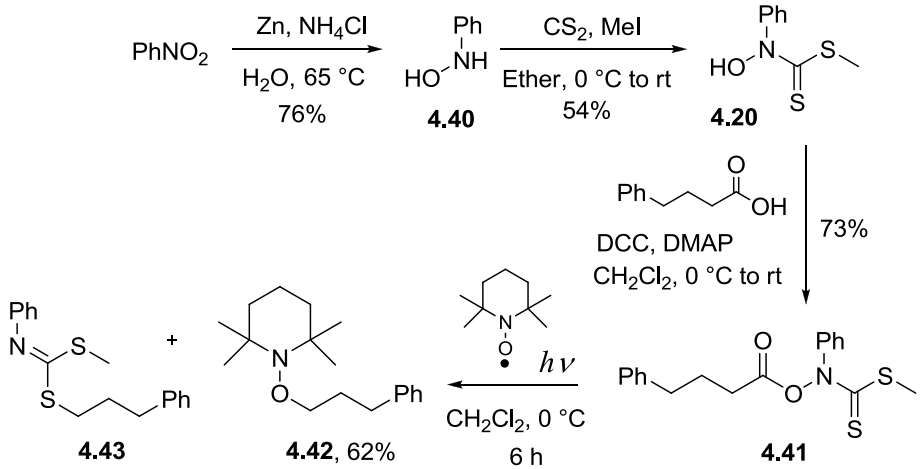
Scheme 4.17 General illustration of photolytic cleavage and trapping of profluorescent nitroxide

4.4 Photocleavable Dithiocarbamate Nitroxides

4.4.1 Synthesis of Dithiocarbamate Nitroxides and Photolysis

Nitroxides bearing MPDOC esters can be prepared from the coupling reaction of the corresponding carboxylic acids and *N*-hydroxy-*S*-methyl-*N*-

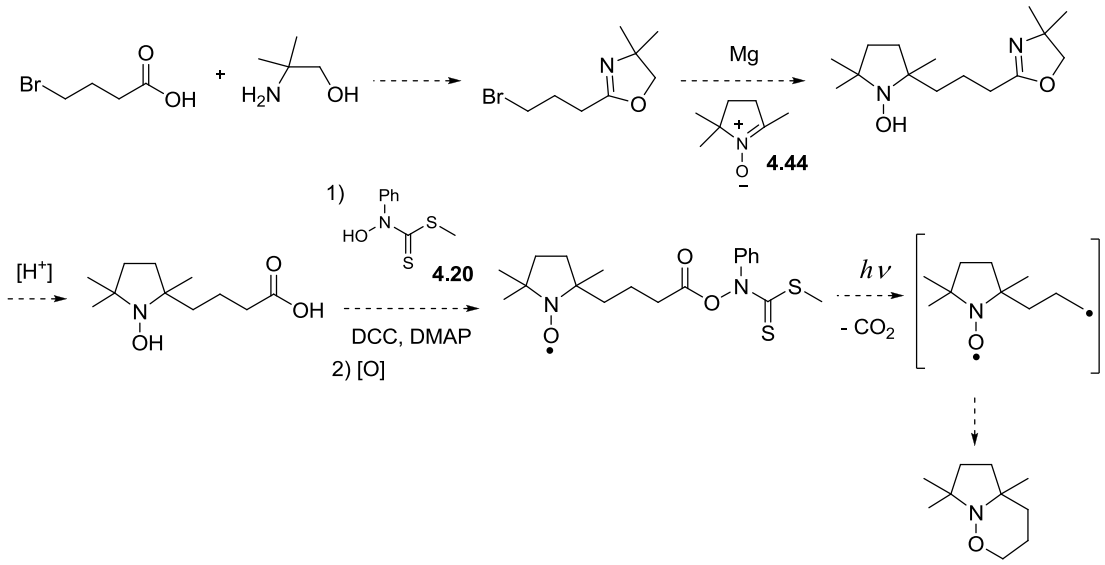
phenyldithiocarbamate **4.20**. Following the procedure of Renaud *et al.*,[17] *N*-phenylhydroxylamine was synthesized by the reduction of nitrobenzene with zinc and ammonium chloride as shown in **Scheme 4.18**. The hydroxylamine **4.40** was obtained in 76% yield after precipitation. Reaction of **4.40** with carbon disulfide, iodomethane and triethylamine afforded *N*-hydroxy-*S*-methyl-*N*-phenyldithiocarbamate **4.20** in 54% yield. In order to perform a model reaction, 4-phenylbutyric acid was coupled with dithiocarbamate **4.20** in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP). Column chromatography provided methyl 4-phenylbutanoyloxy(phenyl)carbamodithioate **4.41**, in 73% yield. With MPDOC ester **4.41** in hand, the intermolecular radical trapping was carried out. Irradiation of a solution of **4.41** and 2,2,6,6-tetramethyl



Scheme 4.18 Synthesis of dithiocarbamate **4.41**, followed by photolysis and trapping with TEMPO

piperidine-1-oxyl (TEMPO) in dichloromethane with a 300 W reflector lamp (Philips) at 0 °C for 9.5 hours afforded the product derived from photolysis following by nitroxide trapping, 1-(3-phenylpropoxy)-2,2,6,6-tetramethylpiperidine **4.42** in 38% yield after column chromatography. The yield was improved to 62% when a medium pressure mercury lamp was used. The rearrangement product **4.43** was also observed by low resolution mass spectrometry (LRMS). This reaction confirmed that the primary radical formed after decarboxylation can be effectively trapped by a nitroxide, even in an intermolecular reaction.

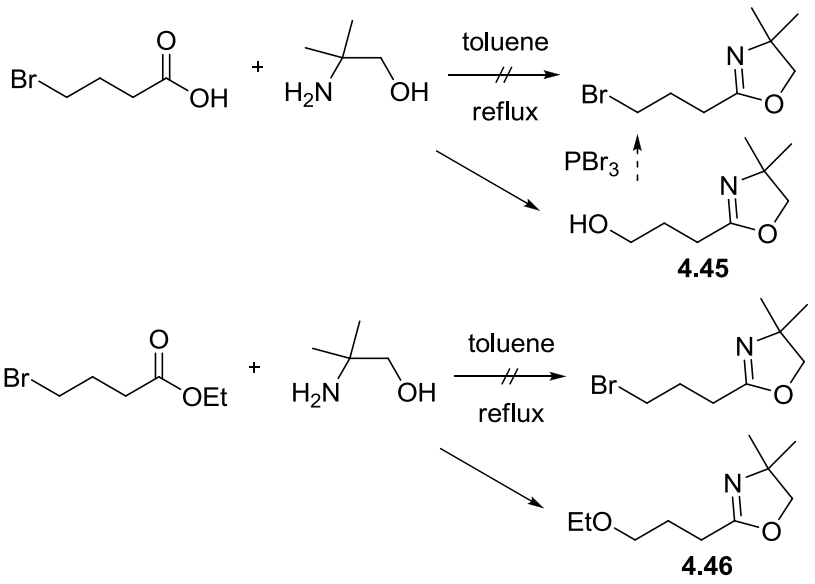
In order to synthesize a nitroxide bearing a pendant MPDOC ester, it was planned that a carboxylic acid with a suitable chain length be protected, converted into a Grignard reagent, and added to nitrone **4.44** (**Scheme 4.19**). The resulting hydroxylamine would be oxidized to give a nitroxide. The carboxylic acid would be deprotected, and then coupled with dithiocarbamate **4.20**. The photolytic cleavage would give a primary radical, which would be trapped intramolecularly by the nitroxide radical to give a six membered ring product.



Scheme 4.19 Proposed synthesis of a nitroxide bearing the MPDOC ester group, followed by photolysis

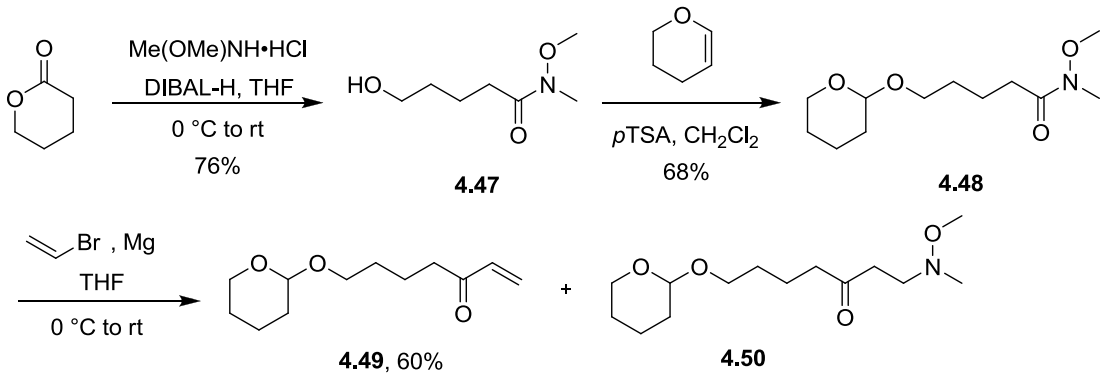
Oxazolines are a useful protecting group for carboxylic acids for use with Grignard and hydride reagents.[24] To convert the carboxylic acid into the oxazoline, 4-bromobutyric acid was refluxed with 2-amino-2-methyl-1-propanol in toluene.[25] The use of ethyl-4-bromobutyrate in place of the acid under the same condition was attractive because of the lower price, and the ease of removing ethanol (**Scheme 4.20**). The resulting product from both substrates gave oxazolines; however unexpectedly the expelled water and ethanol underwent an S_N2 substitution on the alkyl bromide to give the alcohol 3-(4,5-dihydro-4,4-dimethyloxazol-2-yl)propan-1-ol **4.45** and the ethyl ether 2-(3-ethoxypropyl)-4,5-dihydro-4,4-dimethyloxazole **4.46**, as confirmed by NMR and LRMS. The alcohol **4.45** could possibly be turned back into

the alkyl bromide by treatment with phosphorus tribromide.



Scheme 4.20 Attempts to turn the carboxylic acid and ester into a protected oxazoline

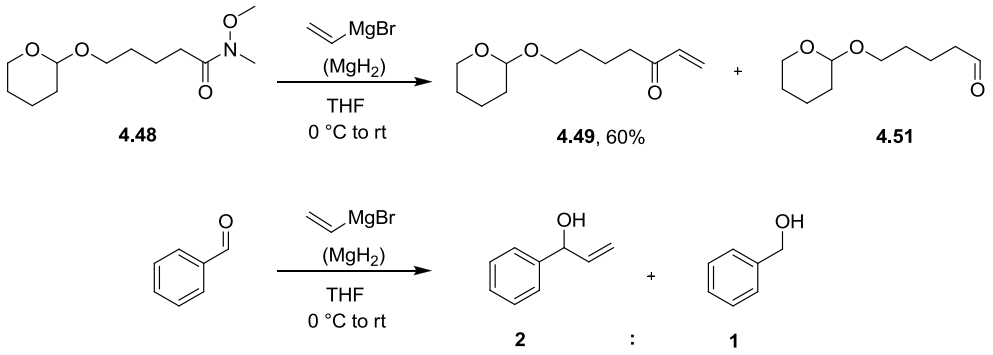
An alternative approach to make a nitroxide bearing a carboxylic acid with a suitable chain length was investigated. Following the general procedure of Huang *et al*.,[26] *N*,*O*-dimethylhydroxylamine hydrochloride was utilized in the presence of DIBAL-H to open the ring of δ-valerolactone to form the Weinreb amide 5-hydroxy-*N*-methoxy-*N*-methylpentanamide **4.47** in 76% yield as shown in **Scheme 4.21**. The hydroxyl group of **4.47** was then protected using 3,4-dihydro-2*H*-pyran in the presence of *p*-toluenesulfonic acid (*p*TSA) to provide *N*-methoxy-*N*-methyl-5-(tetrahydro-2*H*-pyran-2-yloxy) pentanamide **4.48** in 68% yield after column



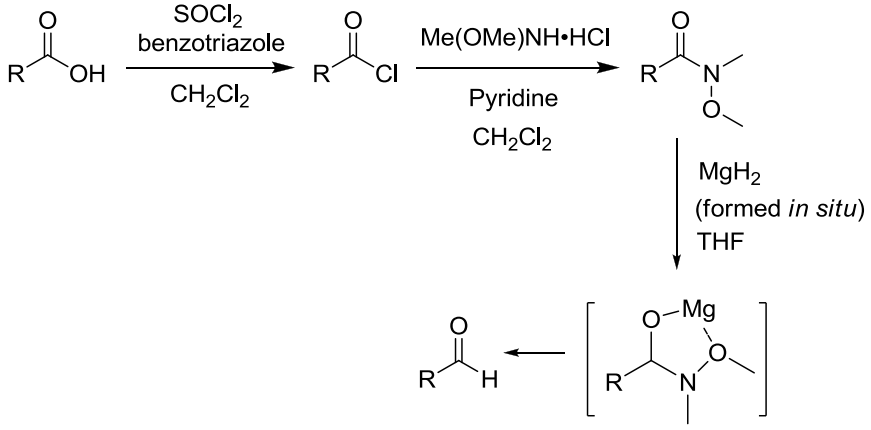
Scheme 4.21 Synthesis of α, β-unsaturated ketone **4.49** from δ-valerolactone

chromatography. An attempt to use the Weinreb amide **4.48** without a protecting group gave a dissappointing low yield in the next reaction, even though the excess Grignard reagent was utilized. The use of *tert*-butyldimethylsilyl (TBDMS) protecting group was also attempted; however slightly wet DMF gave a consistently low yield. As a result, the tetrahydro-2*H*-pyran (THP) protecting group was utilized. The addition of the freshly prepared vinylmagnesium bromide to the THP-protected Weinreb amide **4.48** afforded 7-(tetrahydro-2*H*-pyran-2-yloxy) hept-1-en-3-one **4.49** in a 60% yield after column chromatography. Later, it was found that after quenching with saturated ammonium chloride, the side product of this reaction **4.50** was formed by Michael addition of non-protonated amine to the unsaturated ketone **4.49** (**Scheme 4.21**).[27] To improve the yield, the protecting group which is not sensitive to strong acid quenching and tetrabutylammonium fluoride (TBAF) (used in the following Michael addition) is recommended.

Surprisingly, using commercially available vinylmagnesium bromide provided a mixture of the desired product **4.49** and the aldehyde **4.51**, as shown in **Scheme 4.22**. It was assumed that there was a magnesium hydride species in solution with the vinylmagnesium Grignard reagent. A model reaction was carried out to prove this assumption (**Scheme 4.22**). Addition of commercially available vinylmagnesium bromide to benzaldehyde afforded an approximately 2:1 mixture of the expected allylic alcohol and benzyl alcohol as determined by integration of the ^{1}H NMR spectrum. These results initiated an interesting collaborative investigation with the Singaram lab into the use of magnesium hydride formed *in situ* as a mild and selective reducing agent. Weinreb amides derived from carboxylic acids should be reduced by magnesium hydride to form aldehydes with no over-reduction to the corresponding alcohols, as shown in **Scheme 4.23**. The conditions of the reduction are now being optimized under collaboration with the Singaram lab.



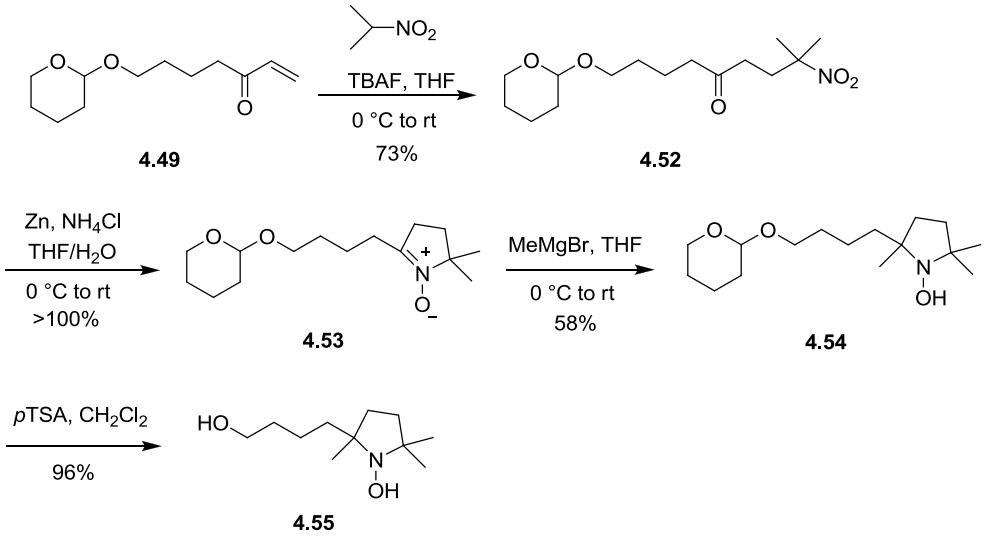
Scheme 4.22 Addition of commercially available vinylmagnesium bromide to Weinreb amide **4.48** gave aldehyde side product **4.51**. Partial reduction of benzaldehyde to benzyl alcohol confirmed the presence of hydride in commercially available vinylmagnesium bromide.



Scheme 4.23 Reduction of carboxylic acids to aldehydes through the corresponding Weinreb amides

To return to the nitroxide synthesis, the nitro compound **4.52** was synthesized via Michael addition of 2-nitropropane to α,β-unsaturated ketone **4.49** in the presence of TBAF as a base, as shown in **Scheme 4.24**. 8-Methyl-8-nitro-1-(tetrahydro-2*H*-pyran-2-yloxy) nonan-5-one **4.52** was obtained in 73% yield after

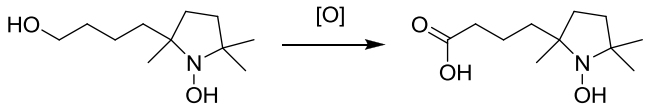
purification by column chromatography. The use of sodium methoxide as a base was avoided because of a competing Michael addition of methoxide to the unsaturated ketone **4.49**. Reduction of **4.52** with zinc and ammonium chloride, following by cyclization afforded 2,2-dimethyl-5-(4-(tetrahydro-2*H*-pyran-2-yloxy) butyl)-3,4-dihydro-2*H*-pyrrole-*N*-oxide **4.53** in >100% crude yield. The nitrone was used in the next reaction without purification. Addition of an excess methyl Grignard reagent to the nitrone **4.53** provided two diastereomers of 2,2,5-trimethyl-5-(4-(tetrahydro-2*H*-pyran-2-yloxy) butyl) pyrrolidin-1-ol **4.54** in 58% yield after column chromatography. Deprotection of the THP group on the alkoxyamine **4.54** by *p*TSA gave 2-(4-hydroxybutyl)-2,5,5-trimethylpyrrolidin-1-ol **4.55** in 96% yield after column chromatography as shown in **Scheme 4.24**.



Scheme 4.24 Synthesis of hydroxylamine **4.55** bearing a primary alcohol from α,β-unsaturated ketone **4.49**

Several attempts to oxidize the alcohol **4.55** directly to the carboxylic acid **4.56** were unsuccessful (**Table 4.1**). Anelli oxidation[28] or oxidation with hydrogen peroxide catalyzed by sodium tungstate[29] gave no reaction. Oxidation with periodic acid (H_5IO_6) catalyzed by pyridinium chlorochromate (PCC),[30] oxidation with Oxone® catalyzed by 2-iodobenzoic acid (2IBAcid),[31] or oxidation with pyridinium dichromate (PDC)[32] caused decomposition of the starting material. Oxidation with IBX and 2-hydroxypyridine (HYP)[33] afforded the corresponding aldehyde.

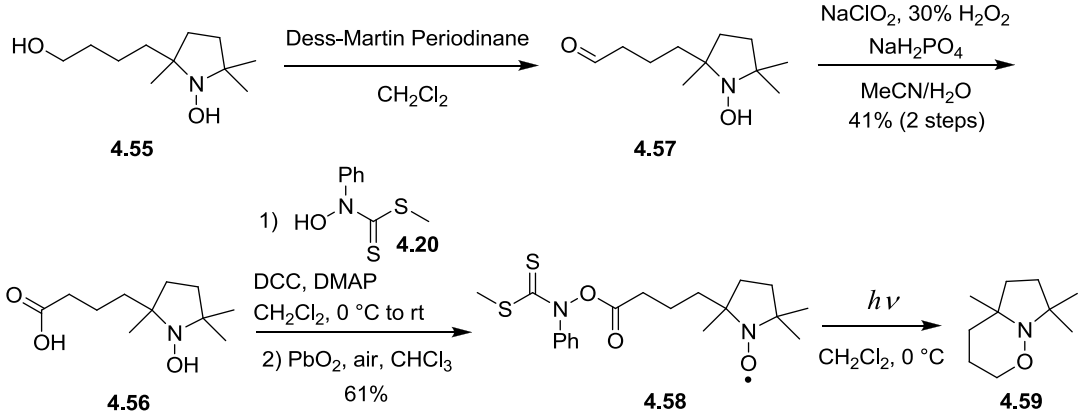
Table 4.1. Attempts of one step oxidations of the alcohol **4.55** to the carboxylic acid **4.56**



4.55 **4.56**

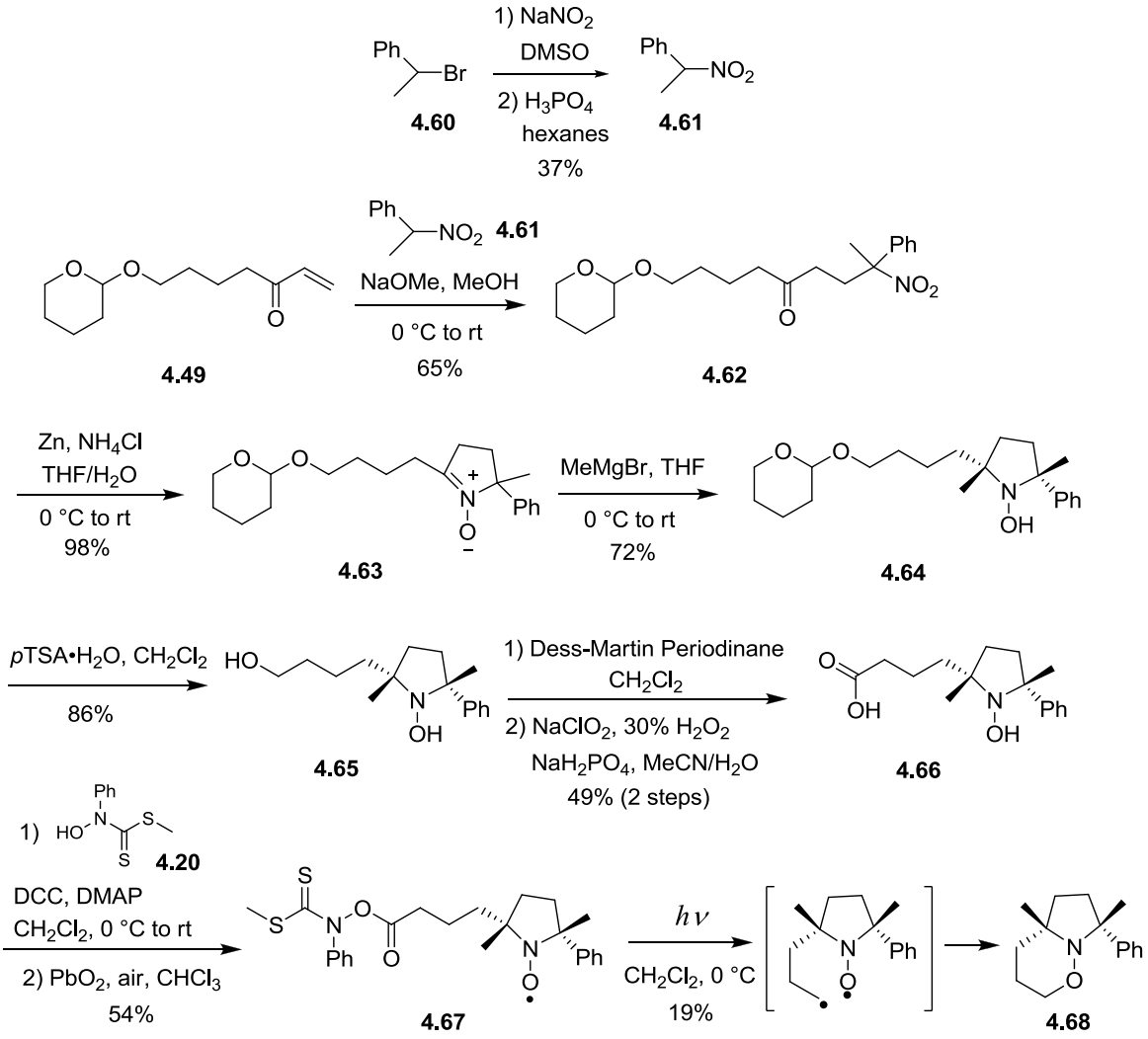
Reagents	Solvent	Conditions	Results
TEMPO, NaOCl, $NaClO_2$, sodium phosphate buffer (Anelli)	MeCN	Heat at 35 °C	No Reaction
H_5IO_6, cat. PCC	MeCN	Room Temperature	Decomposition of the starting material
Oxone®, cat. 2IBAcid	MeCN/H_2O	Heat at 70 °C	Decomposition of the starting material
30% H_2O_2, $NaWO_4 \cdot 6H_2O$, $Bu_4NH_4^+HSO_4^-$	MeOH	Heat at 90 °C	No Reaction
IBX, HYP	DMSO	Room Temperature	Formation of the corresponding aldehyde
PDC	wet DMF	Room Temperature	Decomposition of the starting material
$PhI(OAc)_2$, TEMPO	MeCN/H_2O	Room Temperature	Decomposition of the starting material

Eventually, the oxidation of the alcohol **4.55** to the carboxylic acid **4.56** was achieved by a two step oxidation sequence, as shown in **Scheme 4.25**. First, **4.55** was oxidized to the aldehyde **4.57** using the Dess-Martin periodinane reagent.[32] Without purification, **4.57** was oxidized by sodium chlorite and hydrogen peroxide[34] to the desired carboxylic acid **4.56** in 41% yield over two steps, after column chromatography. The carboxylic acid **4.56** was coupled with dithiocarbamate **4.20**, and then oxidized to give the nitroxide **4.58** in 61% yield. The photolytic cleavage was carried out with a 300 W reflector lamp (Philips) to give a primary radical, which was trapped by the nitroxide radical intramolecularly to afford the six membered ring product **4.59**, as confirmed by the base peak of $[M+1]^+$ = 170.2 in the LRMS. However, the desired product was not found after column chromatography, presumably because the product was lost under high vacuum, similar to sublimation observed with TEMPO and the loss of *N*-butoxy TEMPO under vacuum.[35]



Scheme 4.25 Synthesis of dithiocarbamate ester **4.58** and photolysis to give alkoxyamine **4.59**

In order to solve the problem of volatility, (1-nitroethyl)benzene **4.61** was utilized instead of 2-nitropropane in the Michael addition step to make the final photolytic product non-volatile. Following the procedure of Kornblum and Wade,[36]

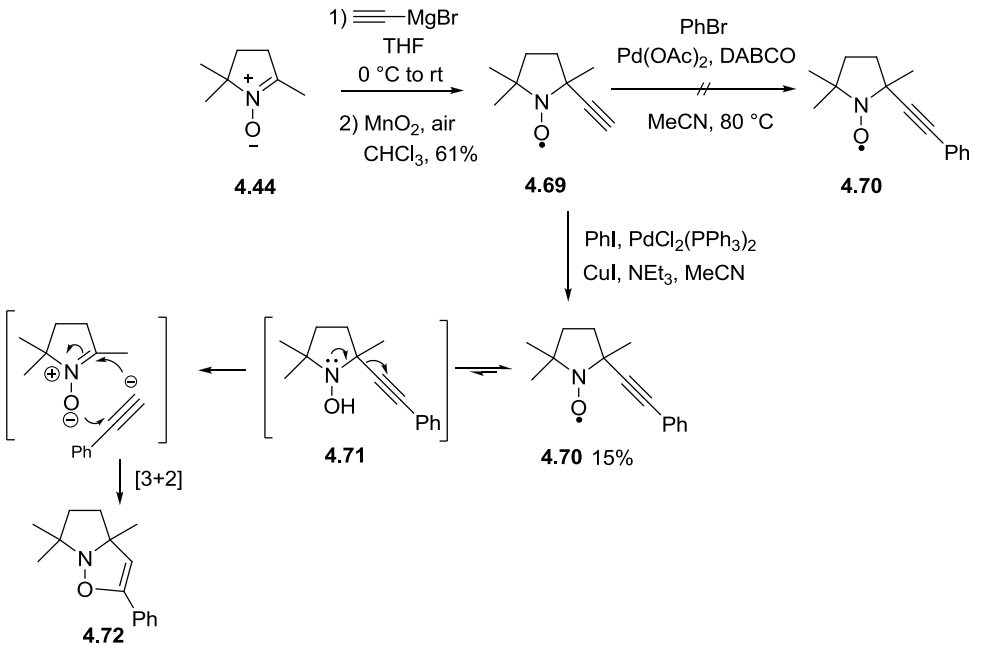


Scheme 4.26 Synthesis of dithiocarbamate ester **4.67** and photolysis to give alkoxyamine **4.68**

nucleophilic substitution of (1-bromoethyl)benzene **4.60** with sodium nitrite provided (1-nitroethyl)benzene **4.61** in 37% yield after distillation (**Scheme 4.26**). Following the same sequence, nitro compound **4.62** were synthesized in 65% yield via Michael addition of (1-nitroethyl)benzene **4.61** to α,β-unsaturated ketone **4.49** in the presence of sodium methoxide. Reduction of **4.62** with zinc and ammonium chloride, following by cyclization afforded nitrone **4.63** in 98% yield without further purification. Addition of an excess of methyl Grignard reagent to the nitrone **4.63** afforded two diastereomers of hydroxylamine **4.64** in 72% yield after column chromatography. Deprotection of the THP group on the alkoxyamine **4.64** by *p*TSA gave alcohol **4.65** in 86% yield after column chromatography. Two-step oxidation of the alcohol **4.65** with Dess-Martin periodinane, following by sodium chlorite and hydrogen peroxide provided the carboxylic acid **4.66** in 49% yield. The carboxylic acid **4.66** was coupled with dithiocarbamate **4.20**, and then oxidized to give the nitroxide **4.67** in 54% yield. Photolytic cleavage of nitroxide **4.67** for 2 hours provided alkoxyamine **4.68** in 19% yield after column chromatography. The relative stereochemistry of **4.68** as shown in **Scheme 4.26** was confirmed by 2D NOESY.

4.4.2 Synthesis of Dithiocarbamate Profluorescent Nitroxide, Photolysis and Fluorescence Studies

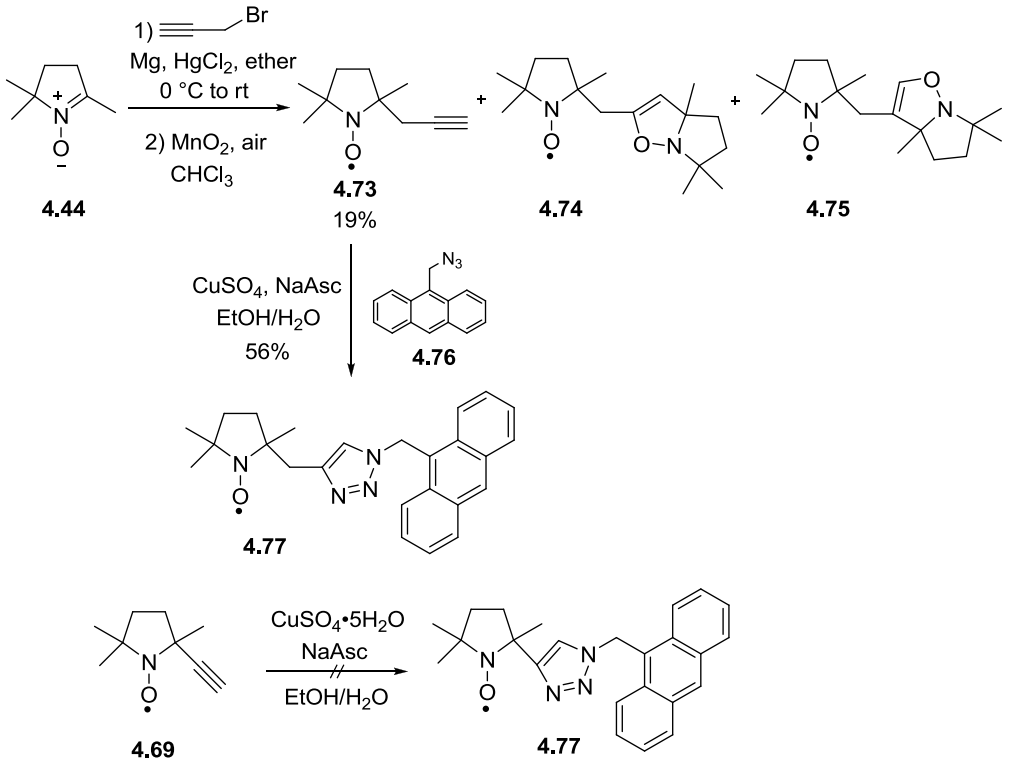
After the success of cyclizing the model photolytic substrate to form product **4.68**, a fluorophore was introduced onto the nitroxide via click chemistry. A model reaction was performed by addition of propargylmagnesium bromide to nitrone **4.44**, followed by oxidation with manganese dioxide to give alkynyl nitroxide **4.69**[37] in 61% yield (**Scheme 4.27**). Synthesis of nitrone **4.44** was previously described in Chapter 3. An attempt to couple the terminal alkyne of **4.69** with bromobenzene under Sonogashira conditions using $Pd(OAc)_2$[38] was unsuccessful. Sonogashira conditions using $PdCl_2(PPh_3)_2$ and CuI[39] gave the desired nitroxide **4.70** in only 15% yield. Approximately 66% of the starting nitroxide **4.69** was recovered. It seems likely that the side product **4.72** resulted from the instability of the hydroxylamine **4.71** (**Scheme 4.27**), which fragment to form nitrone **4.44** and ethynylbenzene anion. Protonation of the anion would form the alkyne, which can then undergo [3+2] cycloaddition[40] to form alkoxyamine **4.72**, explaining the presence of a vinylic proton at 5.09 ppm and a vinylic carbon at 101.3 ppm in the ^{1}H and ^{13}C NMR spectra.



Scheme 4.27 Synthesis of nitroxide **4.70** under Sonogashira coupling conditions

The next attempt to introduce an alkyne into the nitroxide skeleton entailed addition of the Grignard reagent made from propargyl bromide in the presence of $HgCl_2$[41] to nitrone **4.44**, followed by oxidation to give alkynyl nitroxide **4.73** in low yield as shown in **Scheme 4.28**. Hideg *et al*.[40] reported that side products **4.74** and **4.75** were formed via [3+2] cycloaddition between nitrone **4.44** and the desired product **4.73**. With terminal alkyne nitroxide **4.73** in hand, click reaction with anthracene **4.76** (prepared by graduate student Greg O'Bryan) using copper sulfate and sodium ascorbate (NaAsc)[42] afforded profluorescent nitroxide **4.77** in 56% yield. Click reaction between nitroxide **4.69** and anthracene **4.76** under the same

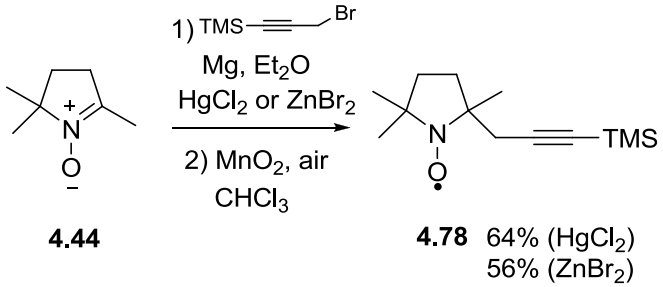
condition was unsuccessful, presumably due to steric hindrance of the neopentyl alkyne.



Scheme 4.28 Synthesis of alkynyl nitroxide **4.73** and subsequent click reaction to form profluorescent nitroxide **4.77**

To improve the yield of propargyl Grignard addition to nitrone **4.44**, 3-bromo-1-(trimethylsilyl)propyne was utilized. Addition of the silyl-protected propargyl Grignard reagent to nitrone **4.44** in the presence of $HgCl_2$[41] or $ZnBr_2$[43] gave satisfactory yields of TMS-protected alkynyl nitroxide **4.78** (**Scheme 4.29**). This

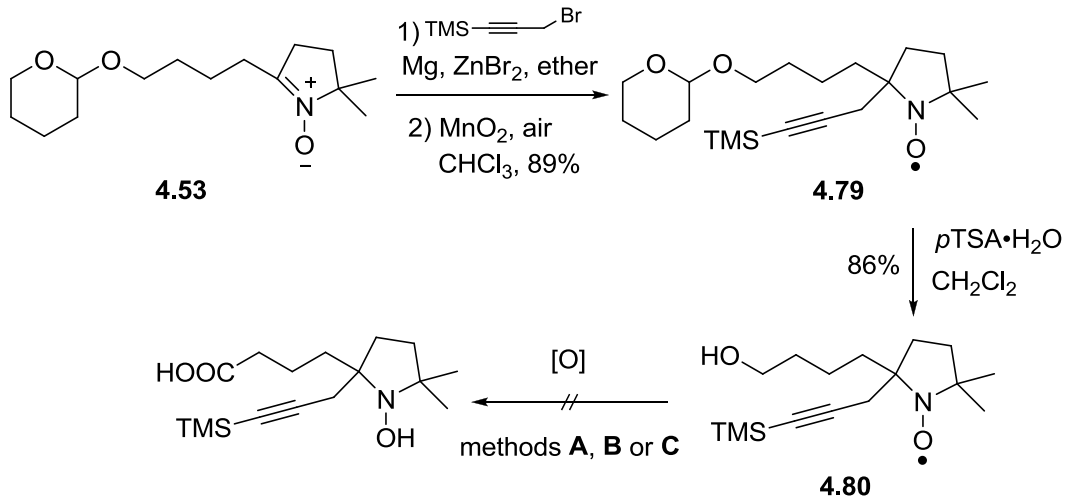
reaction did not give any desired product in THF, but only worked with ether as the solvent.



4.44 **4.78** 64% ($HgCl_2$) 56% ($ZnBr_2$)

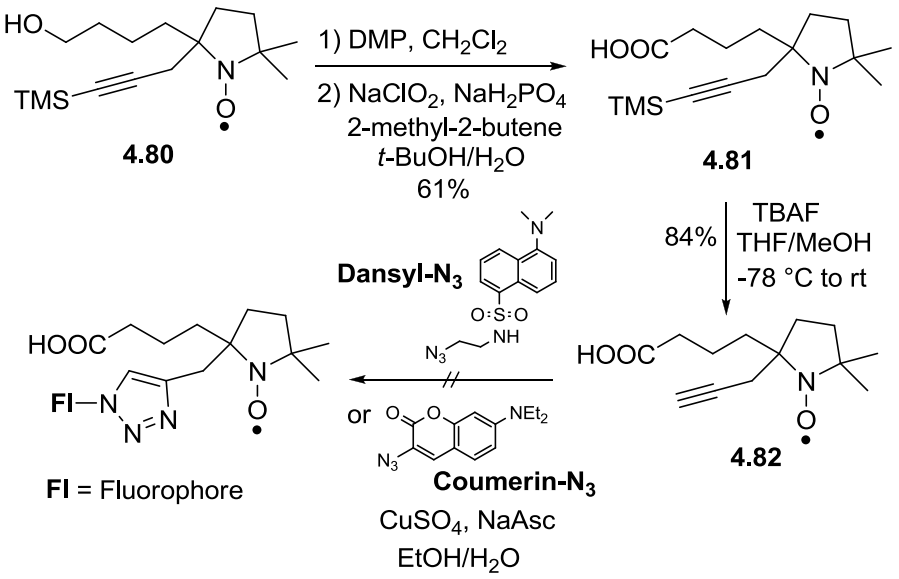
Scheme 4.29 Synthesis of TMS-protected alkynyl nitroxide **4.78**

The $ZnBr_2$ conditions were then applied to the synthesis of a dithiocarbamate profluorescent nitroxide. The Grignard reagent prepared from 3-bromo-1-(trimethylsilyl)propyne was added to nitrone **4.53**, followed by oxidation to afford two diastereomers of the TMS-protected alkynyl nitroxide **4.79** in 89% yield (**Scheme 4.30**). Deprotection of the THP group with *p*TSA provided alcohol **4.80** in 86% yield. Surprisingly, attempts to oxidize alcohol **4.80** to carboxylic acid **4.81** under two-step conditions using sodium chlorite and hydrogen peroxide were unsuccessful. Oxidation with iodobenzene diacetate and iodine[44] or under Ley's condition: $RuCl_3 \cdot 3H_2O$, $NaIO_4$[45] decomposed the starting alcohol.



Scheme 4.30 Synthesis of TMS-protected alkynyl nitroxide **4.80** from nitrone **4.53**

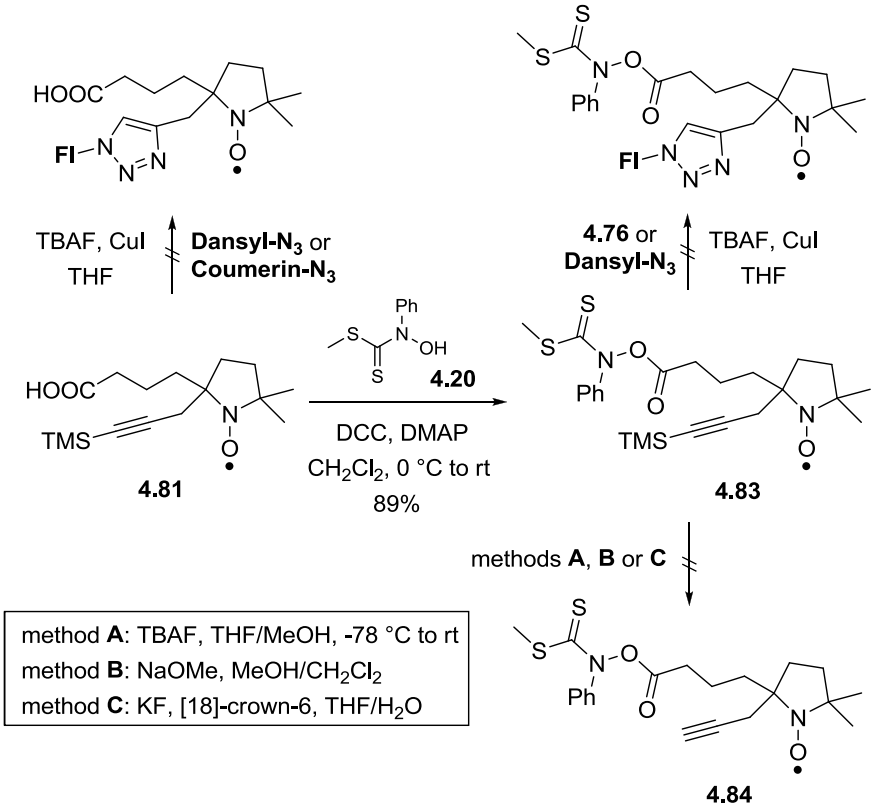
Finally, carboxylic acid **4.81** was obtained by two-step oxidation with Dess-Martin periodinane, followed by Pinnick's oxidation[46] using sodium chlorite in the presence of 2-methyl-2-butene as a scavenger for hypochlorite in 61% yield (**Scheme 4.31**). Deprotection of the TMS group with TBAF afforded alkynyl nitroxide **4.82** in 84% yield. Attempts to "click" alkyne **4.82** with either 2-azido-1-*N*-dansylethylamine (**Dansyl-N_3**) or 3-azido-7-diethylaminocoumarin[47] (**Coumerin-N_3**) using copper sulfate and sodium ascorbate were unsuccessful.



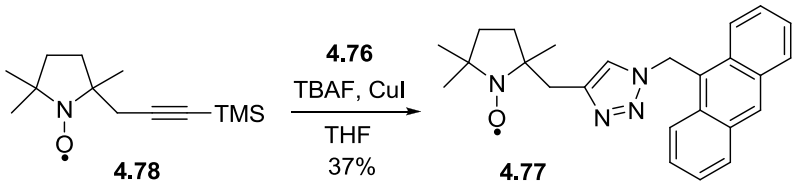
Scheme 4.31 Synthesis of alkynyl nitroxide **4.82** and attempts of click reaction

It was assumed that the failure of the click reaction was due to coordination of the carboxylic acid to the copper. As a consequence, carboxylic acid **4.81** was coupled with dithiocarbamate **4.20** to give dithiocarbamate nitroxide **4.83** in 89% yield as shown in **Scheme 4.32**. To do the click reaction, deprotection of the TMS group with TBAF was attempted, but was unsuccessful. Deprotection using sodium methoxide or potassium fluoride did not give the desired terminal alkyne **4.84**. One-pot deprotection and click reaction of carboxylic acid **4.81** or dithiocarbamate **4.83** with azidodansyl (**Dansyl-N_3**), azidocoumarin (**Coumerin-N_3**) or azidoanthracene **4.76** was also attempted, but all attempts were unsuccessful (**Scheme 4.32**). A

model reaction between nitroxide **4.78** and anthracene **4.76** under the same conditions gave the desired click product **4.77** in 37% yield (**Scheme 4.33**).

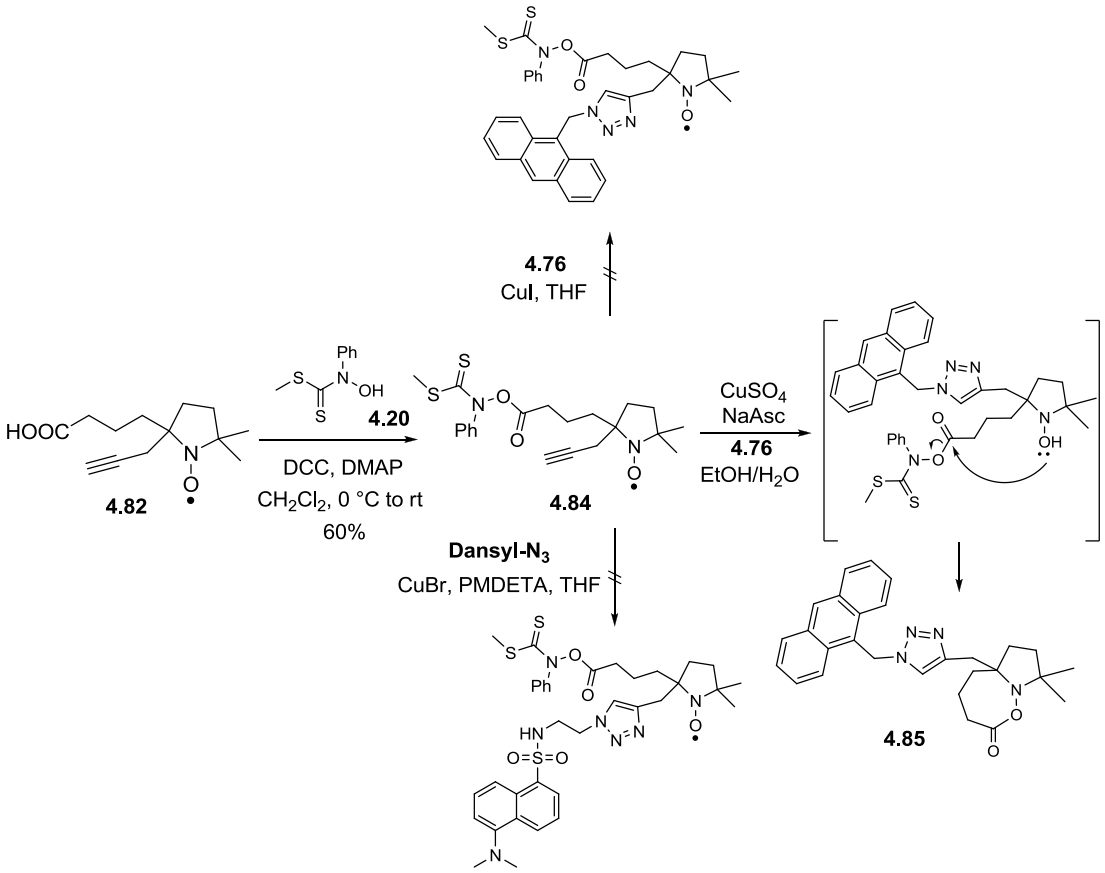


Scheme 4.32 Synthesis of dithiocarbamate **4.83**, attempt to deprotect the TMS group, and attempt to click nitroxides **4.81** or **4.83** with fluorophore azides



Scheme 4.33 Model "click" reaction between nitroxide **4.78** and anthracene azide **4.76**

To avoid deprotection of the TMS group in the presence of the dithiocarbamate ester, nitroxide **4.82** bearing a terminal alkyne was coupled successfully with dithiocarbamate **4.20** to give dithiocarbamate ester **4.84** in 60% yield (**Scheme 4.34**). Alkynyl nitroxide **4.84** did not couple with azidoanthracene **4.76** using copper(I) iodide. Click condition using copper(I) bromide and *N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine (PMDETA) did not provide the desired product.



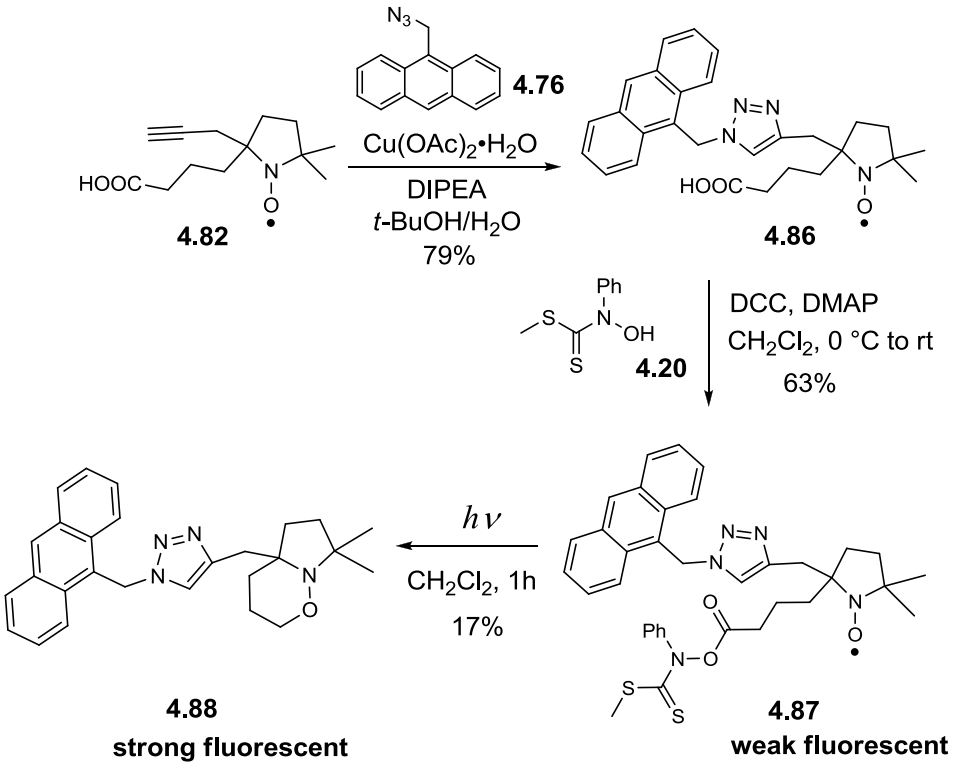
Scheme 4.34 Synthesis of dithiocarbamate nitroxide **4.84** and attempts to carry out click reactions

Copper sulfate and sodium ascorbate enabled the click reaction; however the nitroxide was reduced by sodium ascorbate. The resulting hydroxylamine attacked the carbonyl ester to form a 7-membered ring lactone heterocycle **4.85**.

Zhu *et al*.[48] reported that the chelation-assisted binding between azides bearing auxiliary nitrogen, oxygen or sulfur donor ligands and copper(II) acetate accelerates "click" reaction in alcohol solvents without deliberate addition of a reducing agent such as sodium ascorbate. Alkynyl nitroxide **4.82** bearing a carboxylic acid ligand is expected to assist the click reaction in a similar way. Click reaction between alkynyl nitroxide **4.82** and azidoanthracene **4.76** in the presence of copper acetate and *N*,*N*-diisopropylethylamine (DIPEA) successfully afforded the desired profluorescent nitroxide **4.86** in 79% yield as shown in **Scheme 4.35**. Nitroxide **4.86** was then coupled with dithiocarbamate **4.20** to give the dithiocarbamate profluorescent nitroxide **4.87** in 63% yield. The fluorescence of the tethered anthracene is quenched by the nitroxide, as expected (**Figure 4.1a**).

With the key photocleavable profluorescent nitroxide in hand, photolysis of nitroxide **4.87** in dichlromethane with a high pressure mercury lamp was carried out for one hour. The dithiocarbamate fragmented to give the desired carbon radical, which was trapped by the intramolecular nitroxide as planned. Alkoxyamine **4.88** was obtained in 17% yield after column chromatography (**Scheme 4.35**), which displayed fluorescence emission in the blue region (**Figure 4.1b**). Comparison of

fluorescence emission intensities of **4.87** (**Figure 4.2**, red line) and **4.88** (**Figure 4.2**, purple line) indicates an 6-fold increase in fluorescence after photolysis. Excitation and emission spectra of alkoxylamine **4.88** are blue-shifted from those of profluorescent nitroxide **4.87**.



Scheme 4.35 Click reaction of alkynyl nitroxide **4.82** and azidoanthracene **4.79**, followed by coupling the triazole **4.86** with dithiocarbamate **4.20** provided photocleavable profluorescent nitroxide **4.87**. Photolysis of **4.87** generated a transient carbon radical, which was trapped by the nitroxide to afford strongly fluorescent alkoxyamine **4.88**.

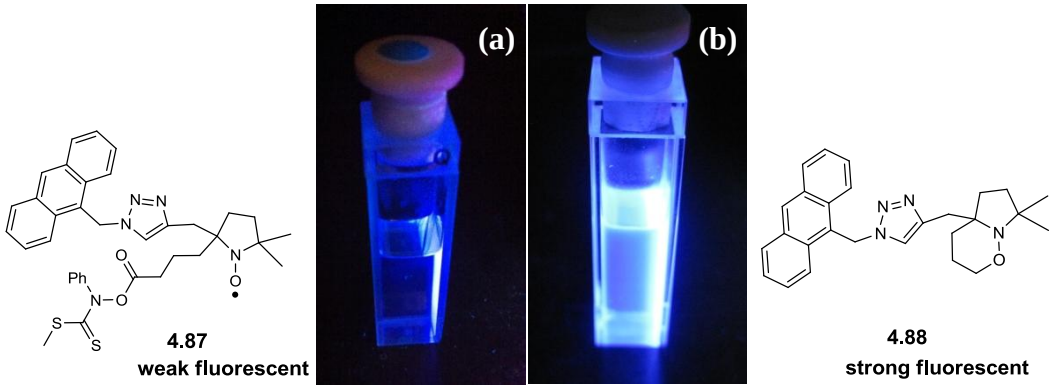


Figure 4.1 Fluorescence upon illumination with a TLC lamp at 366 nm in dichloromethane of **(a)** dithiocarbamate profluorescent nitroxide **4.87**, and **(b)** fluorescent cyclic *N*-alkoxyamine **4.88**

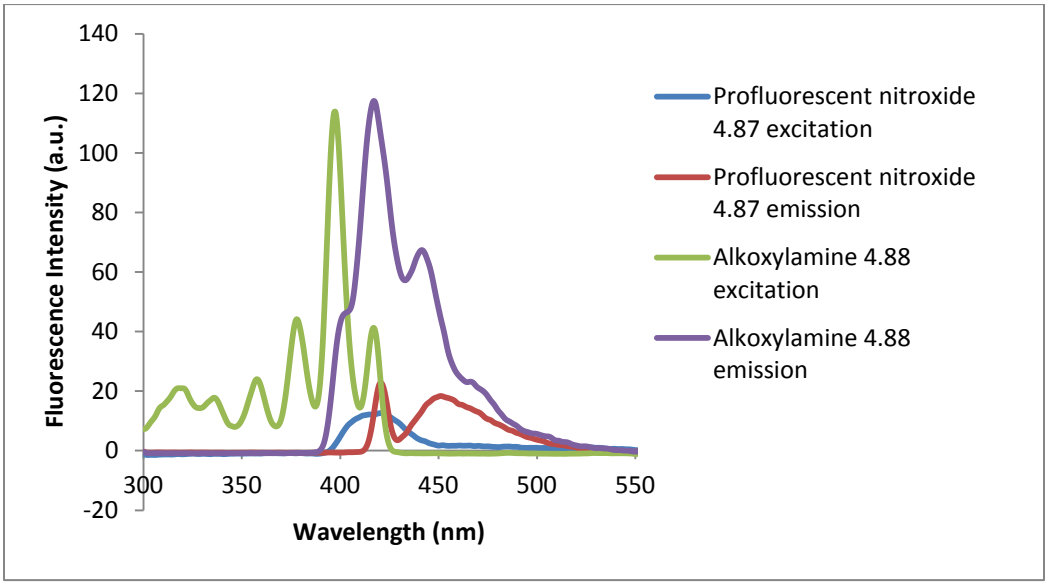
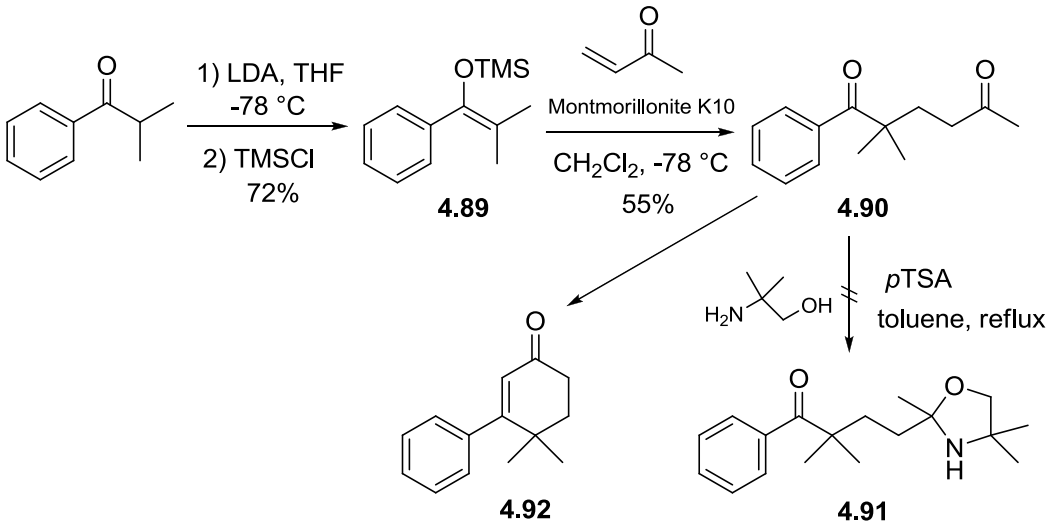


Figure 4.2 Fluorescence spectra in dichloromethane of 3 μM of dithiocarbamate profluorescent nitroxide **4.87** (excitation in blue, emission in red), λ_{ex} = 421 nm, λ_{em} = 451 nm, and fluorescent cyclic *N*-alkoxyamine **4.88** (excitation in green, emission in purple), λ_{ex} = 398 nm, λ_{em} = 417 nm

4.5 Attempted Synthesis of Nitroxides for Norrish Type I Cleavage

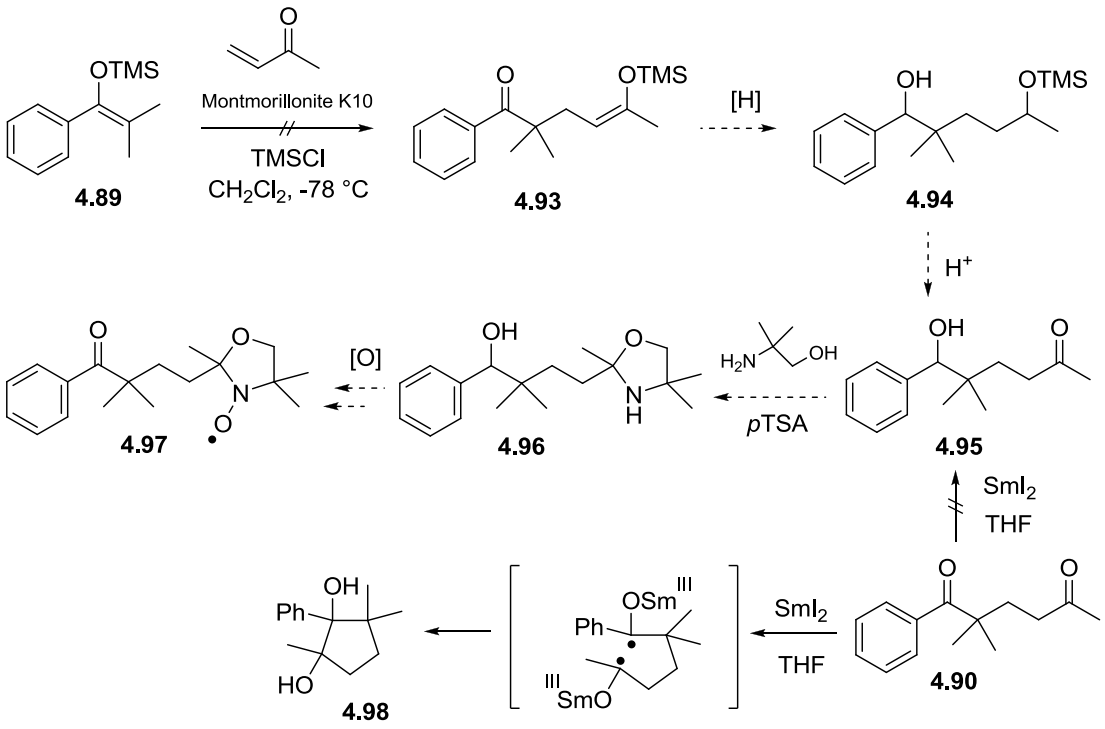
Alternative photosensitive nitroxides were explored bearing side groups which are photolytically cleavable by a Norrish type I mechanism. The nitroxide will trap the tethered radical to form a stable 6-membered ring alkoxyamine. Efforts to synthesize photocleavable doxyl nitroxide **4.97** are shown in **Scheme 4.36** and **Scheme 4.37**. Isobutyrophenone was deprotonated by lithium diisopropylamide (LDA) in tetrahydrofuran, and then trapped by trimethylsilyl chloride to give (2-methyl-1-phenylprop-1-enyloxy) trimethylsilane **4.89** in 72% yield after column chromatography (**Scheme 4.36**).[49] Michael addition of silyl enol ether **4.89** to methyl vinyl ketone in the presence of pre-dried montmorillonite K10 clay (which functions as Brönsted acid) afforded 2,2- dimethyl-1- phenylhexane-1,5-dione **4.90** in 55%



Scheme 4.36 Synthesis of diketone **4.90**, and attempt to condense it with 2-amino-2-methyl-1-propanol

yield.[50] Diketone **4.90** was refluxed with 2-amino-2-methyl-1-propanol in the presence of *p*TSA in toluene, and the water generated was removed via a Dean-Stark trap.[25] The expected aminal product **4.91** was not formed. Instead the Robinson annulation product **4.92** was formed as shown in **Scheme 4.36**.

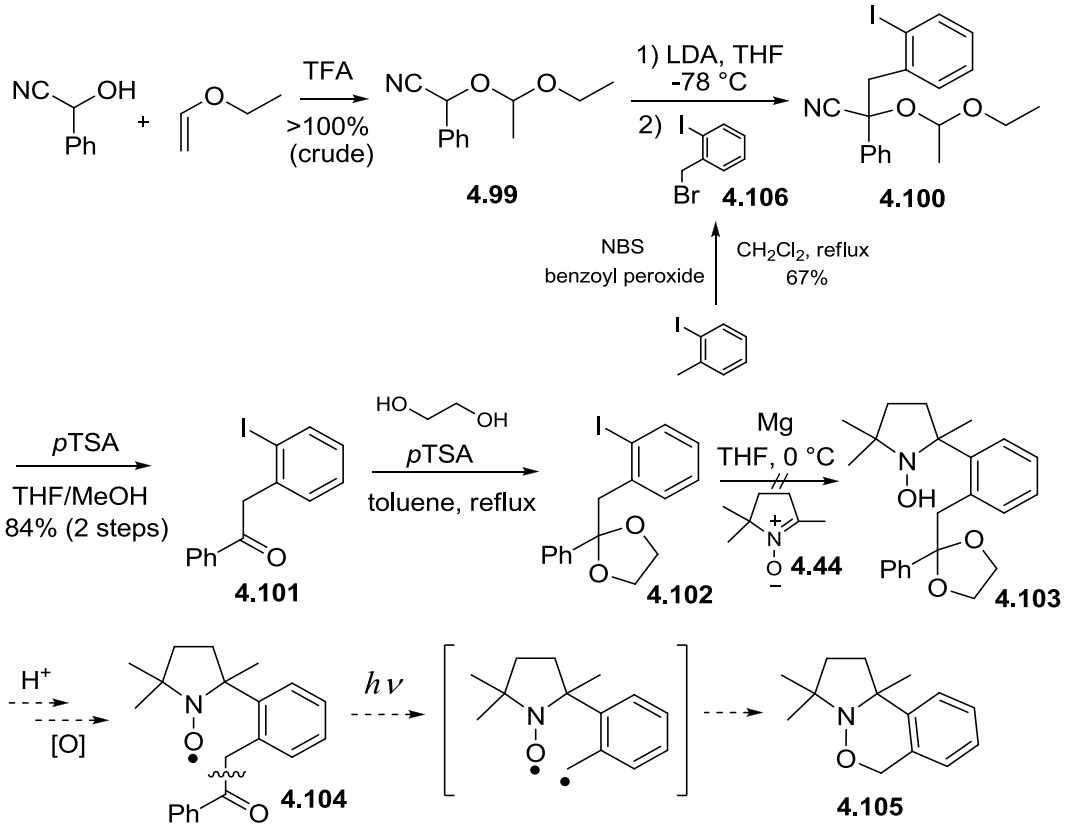
In order to avoid this undesired cyclization, the Michael addition reaction was carried out with trapping to form the silyl enol ether **4.93** (**Scheme 4.37**). The aryl carbonyl would then be reduced to form **4.94** before desilylating to provide **4.95**, following by refluxing with 2-amino-2-methyl-1-propanol to afford **4.96**. Oxidation of **4.96** would give the desired photocleavable doxyl nitroxide **4.97**. Unfortunately, the Michael addition reaction gave the desilylated product **4.90**, although the literature claimed that the acidic pre-dried montmorillonite cannot hydrolyze the silyl enol ether to form the diketone.[51] Single electron reduction using samarium (II) iodide was attempted to chemospecifically reduce the aryl carbonyl of the diketone **4.90** to provide **4.95**. Instead, this reduction yielded the pinacol coupling product **4.98**.



Scheme 4.37 Attempts to make silylated enol ether **4.93** or to selectively reduce diketone **4.90** to form **4.95**

Synthesis of a second designed nitroxide for Norrish type I cleavage was pursued. To tether a photolytically cleavable appendage onto the nitroxide, the side group was made into a good nucleophile that could add to nitrone **4.44**. Following the modified procedure of Watson *et al.*,[52] 2-(1-ethoxyethoxy)-2-phenylacetonitrile **4.99** was synthesized by the reaction of mandelonitrile with ethyl vinyl ether in the presence of trifluoroacetic acid (TFA) as shown in **Scheme 4.38**. Two diastereomers of cyanohydrin **4.99** were obtained in >100% crude yield. Next, deprotonation of **4.99** by LDA, and S_N2 displacement on commercially available 2-iodobenzyl bromide

afforded two diastereomers of 2-(1-ethoxyethoxy)-3-(2-iodophenyl)-2-phenylpropanenitrile **4.100**.[53] Later, 2-iodobenzyl bromide **4.106** was found to be easily synthesized from *o*-iodotoluene, which was 10 times cheaper than purchasing benzyl bromide **4.106**. Bromination of 2-iodotoluene with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide as radical initiator gave 2-iodobenzyl bromide **4.106** in 67% yield after column chromatography (**Scheme 4.38**).



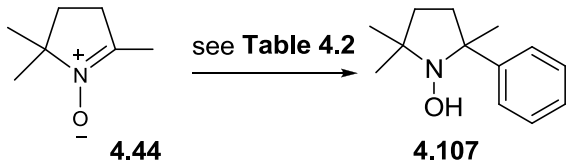
Scheme 4.38 Synthesis of photocleavable side group **4.101**, and attempt to add the derived Grignard to nitrone **4.44**

o-Iodotoluene was not completely consumed, and approximately 25% was usually recovered, even though the reaction mixture was allowed to reflux for 4 days.

Several attempts to deprotect the hidden ketone functional group in **4.100** including the use of 10% hydrochloric acid, 90% TFA,[54] and 1.00 : 0.75 : 0.5 mixture of acetonitrile/0.5N hydrochloric acid/water[55] were unsuccessful. Eventually, the ketone was successfully deprotected by Jones oxidation. However column chromatography was required to get rid of the by-product. When the conditions were changed to *p*-toluenesulfonic acid in a 2:1 mixture of tetrahydrofuran/methanol, deprotection afforded 2-(2-iodophenyl)-1-phenylethanone **4.101** in 84% yield (based on **4.99**) without requiring purification (**Scheme 4.38**). The ketone **4.101** was then protected by refluxing with ethylene glycol in the presence of *p*TSA in toluene to provide 4-(2-iodobenzyl)-4-phenyl-1,2-dioxolane **4.102** in 94% yield after column chromatography. An attempt to make a Grignard reagent from aryl iodide **4.102** with magnesium, following by the nucleophilic addition to nitrone 2,2,5-trimethyl-3,4-dihydro-*2H*-pyrrol-1-oxide **4.44** to form hydroxylamine **4.103** was unsuccessful: both starting materials were recovered. It was planned that deprotection of the ketal, followed by oxidation of the hydroxylamine would form photosensitive nitroxide **4.104**. Norrish type I cleavage, followed by cyclization would have provided alkoxyamine **4.105**.

Subsequently, several attempts were made to achieve the nucleophilic addition of the Grignard reagent formed from iodobenzene to nitrone **4.44** as a model reaction as shown in **Table 4.2**. Following the procedure of Hideg *et al*.,[56] a solution of phenyl Grignard reagent formed from iodobenzene and magnesium was refluxed with nitrone **4.44**. Addition of trimethylsilyl chloride (TMSCl) to make the nitrone more electrophilic and 1,4-diazabicyclo[2.2.2]octane (DABCO) to break a possible organomagnesium aggregates gave only a trace amount of the desired product. Commercially available phenylmagnesium bromide was added to nitrone **4.44** under refluxing THF. Again, only a trace of the product was detected. The next attempt used 5 equivalents of phenylmagnesium bromide at 0 °C to give the desired alkoxyamine, 1-hydroxy-2,5,5-trimethyl-2-phenylpyrrolidine **4.107** in 43% yield. Attention was turned back to the model reagent iodobenzene. Lithiation of iodobenzene with *n*-butyllithium, followed by addition to the nitrone was also unsuccessful. Finally, following the procedure of Pahari and Rohr,[57] Grignard exchange between iodobenzene and isopropylmagnesium chloride, followed by addition to nitrone **4.44** afforded **4.107** in a 50% crude yield.

Table 4.2 Conditions explored for nucleophilic addition of a phenyl group to nitrone **4.44** to form hydroxylamine **4.107**

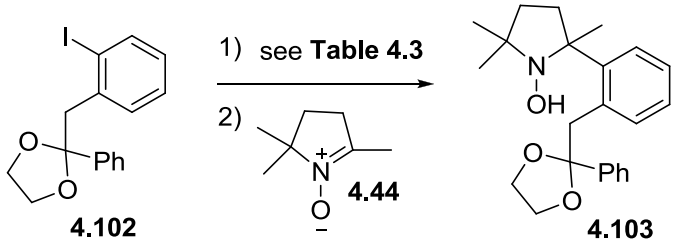


4.44 **4.107**

Reagents	Solvent	Conditions	Results
Iodobenzene, Mg	ether	0 °C to reflux	Trace amount of product formed
Iodobenzene, Mg, TMSCl, DABCO	THF	0 °C to reflux	Trace amount of product formed
PhMgBr	THF	0 °C to reflux	No reaction
PhMgBr (5 equivalents)	THF	0 °C	43% yield
Iodobenzene, *n*-BuLi	THF	-78 °C	No reaction
Iodobenzene, *i*-PrMgCl	THF	0 °C	50% crude yield

Multiple attempts were made to achieve the nucleophilic addition of the Grignard reagent prepared from the aryl iodide **4.102** to nitrone **4.44** as shown in **Table 4.3**. The Grignard exchange between **4.102** and isopropylmagnesium chloride was unsuccessful, and starting material was recovered. Lithiation or lithium-halogen exchange was successful in de-iodinating **4.102**, but addition to the nitrone was unsuccessful, even when the reaction mixture was heated to 35 °C or TMSCl was added. The de-iodinated form of **4.102** was confirmed by observation of the change of the methylene proton chemical shift from 3.4 to 3.2 ppm in the ^{1}H NMR spectrum, and by LRMS. As a consequence, nitrone **4.44** was considered too sterically hindered for the addition of **4.102**.

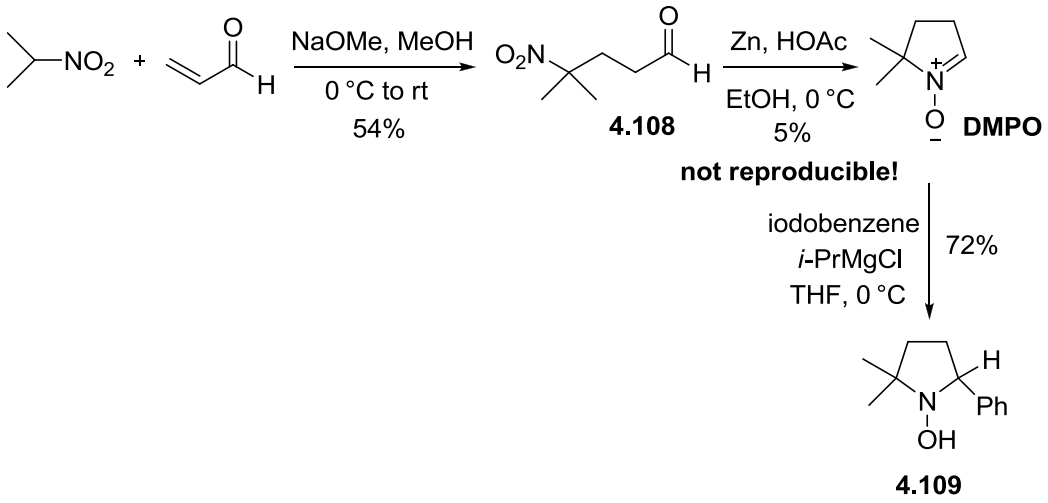
Table 4.3 Attempts of nucleophilic addition of the Grignard or organolithium derived from **4.102** to nitrone **4.44**



Reagents	Solvent	Conditions	Results
i-PrMgCl	THF	-10 °C to 0 °C	No reaction
n-BuLi, $MgBr_2$	THF	0 °C	No addition
n-BuLi, $MgBr_2$	ether	0 °C	No addition
n-BuLi, $MgBr_2$	THF	35 °C	No addition
n-BuLi, $MgBr_2$, TMSCl	THF	0 °C	No addition
n-BuLi	THF	-78 °C	No addition

The next approach was to synthesize the less sterically hindered nitrone 5,5-dimethyl-1-pyrroline-1-oxide (DMPO). As shown in **Scheme 4.39**, 4-methyl-4-nitro-pentanal **4.108** was prepared from the Michael addition of 2-nitropropane to acrolein in the presence of sodium methoxide in methanol. Distillation afforded the nitroaldehyde **4.108** in 54% yield. Reduction of **4.108** with zinc and ammonium chloride following by cyclization to form DMPO was unsuccessful. Glacial acetic acid was used instead of ammonium chloride,[58] but this procedure was not effectively reproducible. The best result gave DMPO in only 5% yield after column chromatography. It was reported that the difficulty in this reduction is probably due

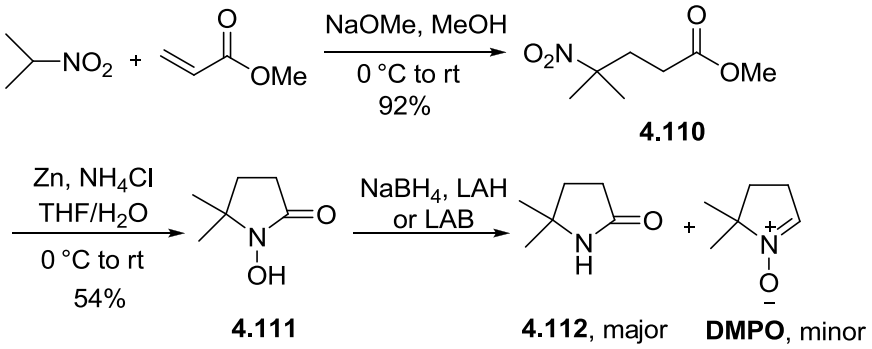
to competing nitroaldehyde polymerization, rather than any effect of the zinc.[59] The Grignard exchange between iodobenzene and isopropylmagnesium chloride, following by the addition to DMPO was carried out to provide 2,5-dimethyl-1-hydroxy -2-phenylpyrrolidine **4.109** in 72% yield as shown in **Scheme 4.39**.



Scheme 4.39 Synthesis of DMPO and Grignard addition to form hydroxylamine **4.109**

Due to the non-reproducibility of this preparative route, an alternative method to make DMPO was attempted as shown in **Scheme 4.40**. The reaction of 2-nitropropane with methyl acrylate in the presence of sodium methoxide in methanol afforded methyl 4-methyl-4-nitropentanoate **4.110** in 92% yield. Reduction of nitroester **4.110** with zinc and ammonium chloride in a mixture of tetrahydrofuran and water gave 5,5-dimethyl-1-hydroxy-2-pyrrolidinone **4.111** in 54% yield.

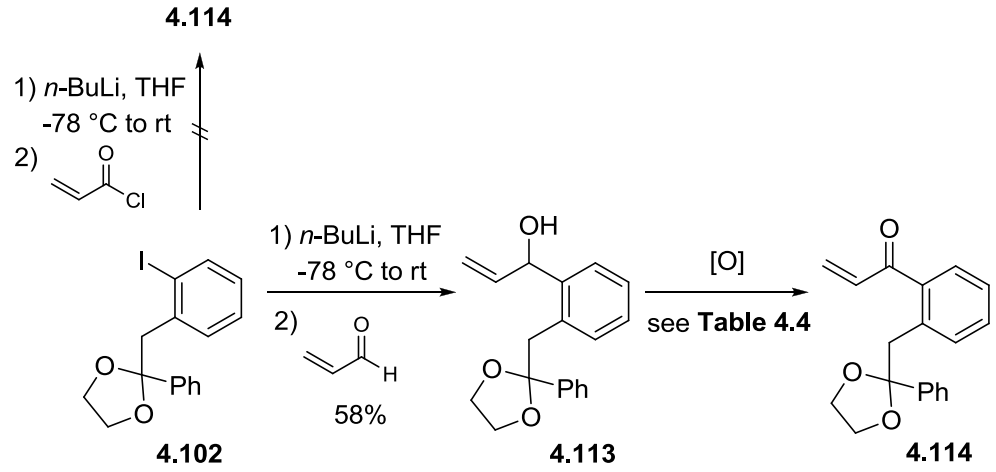
Attempts to reduce this hydroxamic acid, including the use of sodium borohydride ($NaBH_4$) in methanol, lithium aluminum hydride (LAH) in refluxing toluene, LAH in cold THF, and lithium aminoborohydride (LAB) in cold THF were unsuccessful. In the first three cases, cleavage of the N-O bond of hydroxamic acid **4.111** was the major reaction, while the reduction afforded just a minor amount of the desired nitrone product as confirmed by ^1H NMR, IR, and LRMS. N-O bond cleavage to form **4.112** was also observed when the reduction of the nitroester **4.110** was allowed to run for a long period of time, or when a large amount of zinc powder was added.



Scheme 4.40 Attempted synthesis of DMPO from hydroxamic acid **4.111**

Since either the photocleavable side group or the nitrone are too sterically hindered for nucleophilic addition, and synthesis of the less sterically hindered nitrone DMPO resulted in a very low yield and was not reproducible, a new strategy was pursued: introduction of the precursor of the nitrone to the photolytically

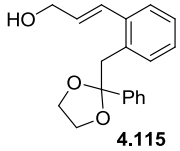
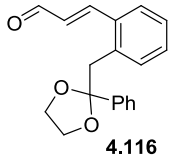
cleavable side group. Nucleophilic acyl substitution of the organolithium derived from **4.102** to acryloyl chloride was unsuccessful, presumably due to a second addition of organolithium to the more reactive α,β-unsaturated ketone product **4.114** (**Scheme 4.41**). The next attempt entailed nucleophilic addition to acrolein to give 1-(2-((2-phenyl-1,3-dioxolan-2-yl) methyl) phenyl) prop-2-en-1-ol, **4.113** in 58% yield after column chromatography. Several attempts were carried out to achieve



Scheme 4.41 Synthesis of allylic alcohol **4.113** from aryl iodide **4.102**

the oxidazion the allylic alcohol **4.113** to the α,β-unsaturated ketone **4.114**, as shown in **Table 4.4**. The use of air and MnO_2 as a catalyst afforded only a small amount of the product. The yield was not improved even though the reaction mixture was refluxed,[60] sonicated, or the solvent was switched from Et_2O[61] to CH_2Cl_2,[62,63] EtOAc[64] or MeCN.[65] Swern oxidation[66] provided a mixture of the desired

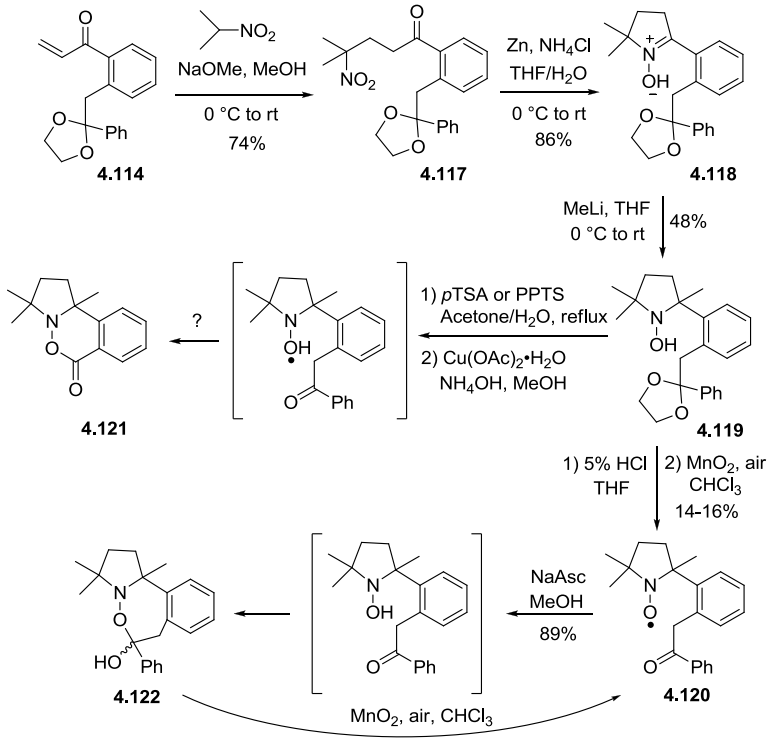
Table 4.4 Oxidations of allylic alcohol **4.113** to α, β-unsaturated ketone **4.114**

Reagents	Solvent	Conditions	Results
MnO_2	Ether, CH_2Cl_2, EtOAc or MeCN	RT	Low yield
MnO_2, O_2 (air)	EtOAc	Sonication	Low yield
MnO_2	CH_2Cl_2 or EtOAc	Reflux	Low yield
$(COCl)_2$, DMSO, NEt_3 (Swern)	Dry CH_2Cl_2	-78 °C to RT	Mixture of product and  **4.115**
t-BuOOH, cat. CrO_3	CH_2Cl_2	RT	Decomposition of starting material
PCC	CH_2Cl_2	RT	Decomposition of starting material
DMP	CH_2Cl_2 (slightly wet)	RT	Mixture of product and  **4.116**
DMP	Dry CH_2Cl_2	RT	74% yield
IBX	EtOAc	Reflux	Mixture of product and trace amount of starting material

unsaturated ketone **4.114** and the product of allyl inversion, unsaturated alcohol **4.115** as the side product. It was assumed that the DMSO used was slightly wet, so water attacked an allylic cation intermediate to give the undesired allylic inversion product **4.115**. Oxidation using pyridinium chlorochromate (PCC) or *tert*-butyl peroxide and catalytic chromium trioxide[67] led to the decomposition of the starting material. Dess-Martin periodinane (DMP) reagent in slightly wet CH_2Cl_2 gave a mixture of the product and the undesired aldehyde **4.116**, which was derived from

alcohol **4.115**. Gratifyingly, use of 2-iodoxybenzoic acid (IBX) in refluxing EtOAc,[68] or DMP in anhydrous CH_2Cl_2[69,70] provided the desired unsaturated ketone **4.114**, but the IBX oxidation was not complete. DMP oxidation was chosen to obtain 1-(2-((2-phenyl-1,3-dioxolan-2-yl) methyl) phenyl) prop-2-en-1-one **4.114** in 74% yield, because it was feared that the heat required for the IBX oxidation might cause polymerization of the product.

With successful oxidation conditions in hand, nitro compound **4.117** was synthesized by Michael addition of 2-nitropropane to α,β-unsaturated ketone **4.114** in the presence of sodium methoxide as shown in **Scheme 4.42**. As there is Michael

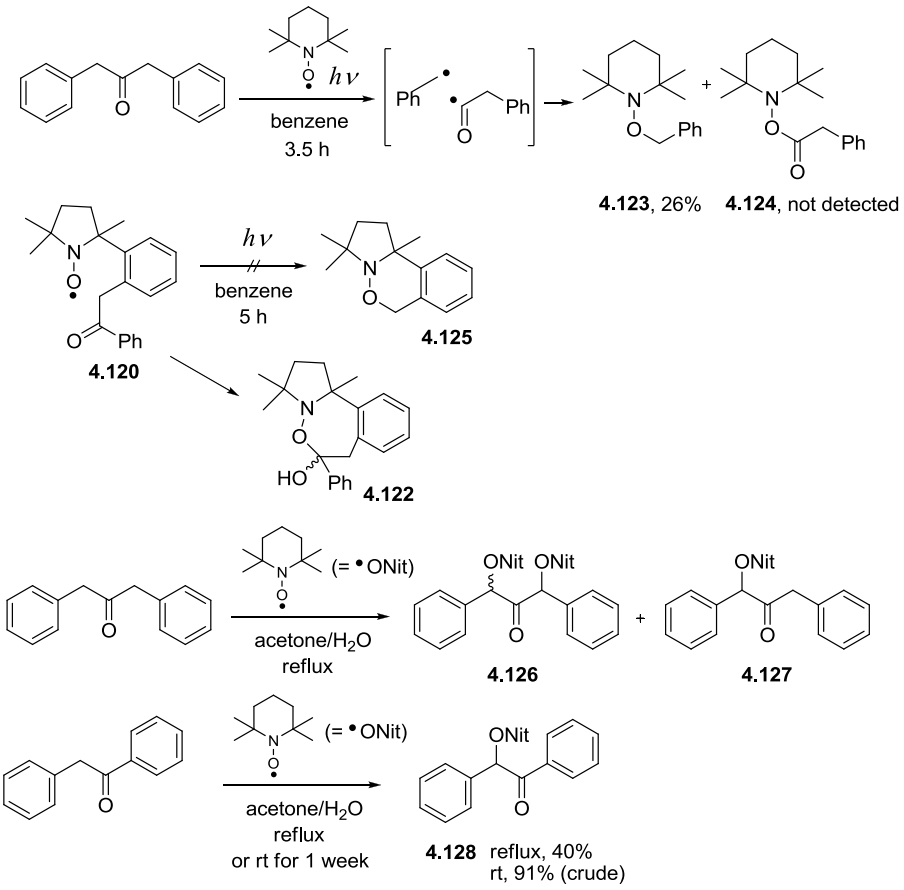


Scheme 4.42 Synthesis of photosensitive nitroxide **4.120** for Norrish type I cleavage

addition of methoxide to α, β-unsaturated ketone **4.114**, use of TBAF as a base is recommended. Recrystallization in hexanes provided 4-methyl-4-nitro-1-(2-((2-phenyl-1,3-dioxolan-2-yl) methyl) phenyl) pentan-1-one **4.117** in 74% yield. Reduction of **4.117** with zinc and ammonium chloride, following by cyclization afforded 2,2-dimethyl-5-(2-((2-phenyl-1,3-dioxolan-2-yl) methyl) phenyl)-3,4-dihydro-2*H*-pyrrole 1-oxide **4.118** in 86% yield after recrystallization. An attempt to add methyl Grignard reagent to nitrone **4.118** was unsuccessful, even when trimethylsilyl chloride (TMSCl) was added to increase the electrophilicity of the nitrone. However, a large excess (10 equivalents) of a stronger methyl nucleophile, methyl lithium, was successfully added to this nitrone to provide 2,2,5-trimethyl-5-(2-((2-phenyl-1,3-dioxolan-2-yl) methyl) phenyl) pyrrolidin-1-ol **4.119** in 48% yield after column chromatography. Deprotection of the ketal group, followed by mild oxidation unexpectedly afforded cyclic ester **4.121** instead of the desired nitroxide **4.120** (**Scheme 4.42**). The identity of the unexpected product **4.121** was confirmed by ^{1}H and ^{13}C NMR spectra, 2D NMR, and LRMS. The mechanism to form cyclic ester **4.121** is unclear. Switching deprotection condition to 5% hydrochloric acid, following by oxidation provided the desired nitroxide **4.120** in low yields (16%) as shown in **Scheme 4.42**. In these cases, starting material **4.119** was recovered. When benzyl ketone nitroxide **4.120** was reduced by sodium ascorbate in methanol, the formation of ketal **4.122**, resulting from the reduction of the nitroxide, followed by

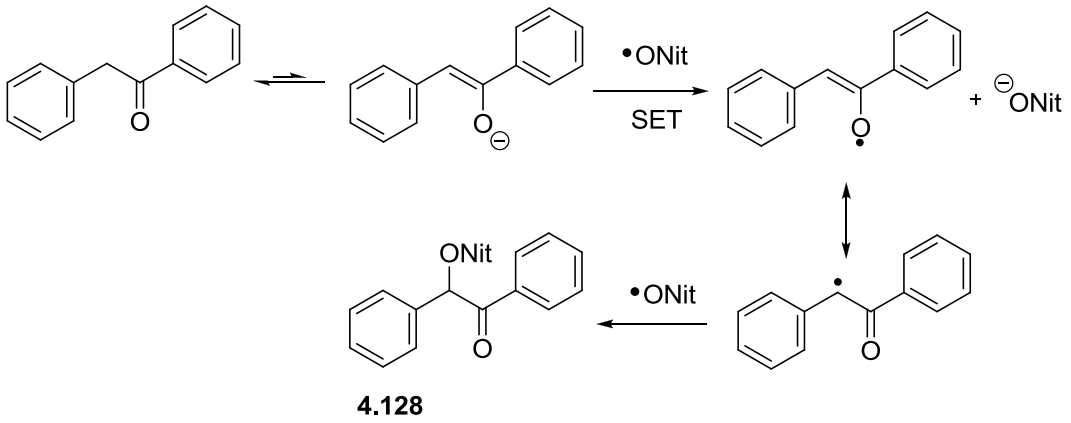
cyclization was observed. If the fluorophore was appended to this nitroxide, it would be a potential profluorescent nitroxide detector for reducing agents (*vide infra*). To reform the nitroxide, oxidation with manganese dioxide open to the atmosphere for approximately three days is required.

As a model reaction for Norrish type I cleavage, photolysis of 1,3-diphenylacetone in the presence of TEMPO was carried out with medium pressure



Scheme 4.43 Photolysis of 1,3-diphenylacetone and nitroxide **4.120**. Formation of alkoxyamines **4.126**, **4.127** and **4.128** from benzyl ketones.

mercury lamp for 3.5 hours (**Scheme 4.43**). The expected alkoxyamine **4.123** was obtained in 26% yield, but alkoxyamine **4.124** was not detected. Unfortunately, photolysis of nitroxide **4.120** in benzene did not give the desired Norrish type I cleavage product **4.125**. After column chromatography, the acetal **4.122** was isolated in 31% yield. It is possible that the nitroxide radical quenches the excited triplet state of the ketone, and thus prevents Norrish type I cleavage. Instead it appears that nitroxide **4.120** was photo-reduced to the hydroxylamine, which added to the ketone to form the acetal **4.122**. Under thermal conditions, 1,3-diphenylketone or 2-phenylacetophenone were refluxed with TEMPO in aqueous acetone to give alkoxyamines **4.126**, **4.127**, and **4.128**, as shown in **Scheme 4.43**. Alkoxyamine **4.128** was also formed in 91% crude yield even at room temperature after 2-phenylacetophenone and TEMPO in acetone was stirred open to the atmosphere for one week. These reactions presumably occur via single electron transfer (SET) between the enolate and a nitroxide to form an α-carbonyl radical and a hydroxylamine anion. Nitroxide trapping would then give the product as shown in **Scheme 4.44**. This type of reaction has been reported previously by Tan *et al*.[71] in the α-alkoxyamination of 1,3-dicarbonyl compounds by TEMPO using photocatalyzed Rose Bengal.



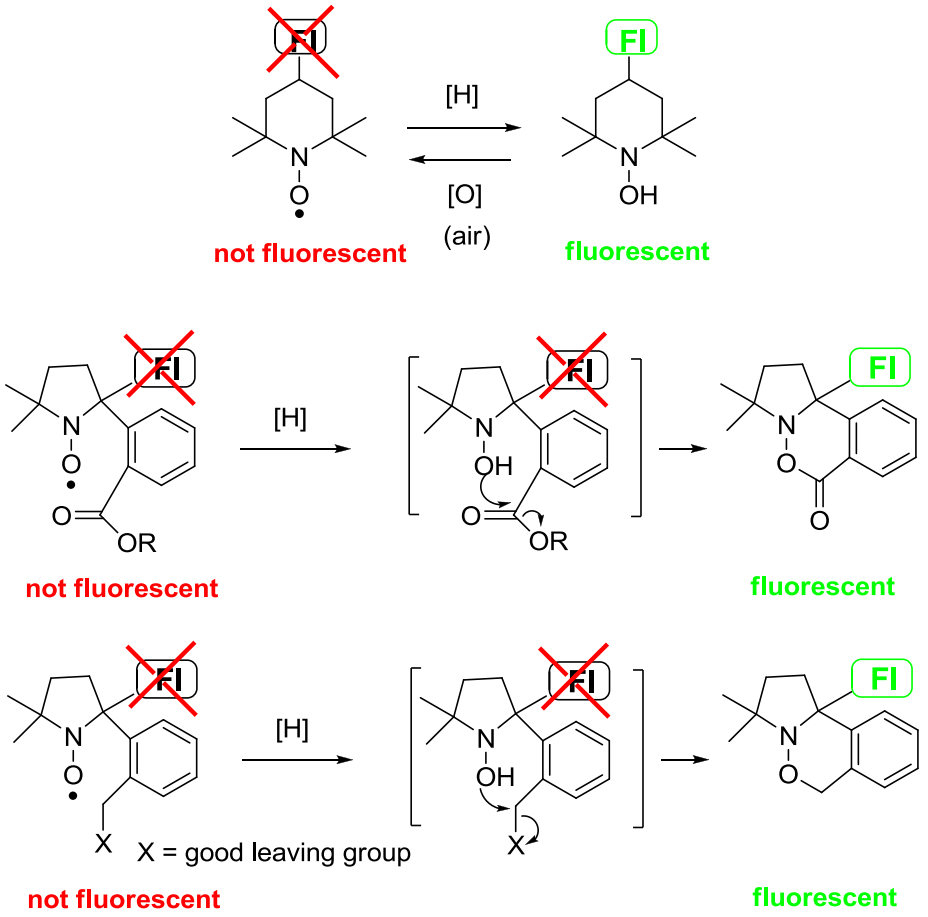
4.128

Scheme 4.44 Single electron transfer (SET) between the enolate and a nitroxide to form, followed by nitroxide trapping to form alkoxyamine **4.128**

4.6 Profluorescent Nitroxide as a Probe for Reducing Agents

As nitroxides can be reduced to hydroxylamines by mild reducing agents, various profluorescent nitroxides have been utilized in the detection of reductants. Naturally occurring antioxidants including ascorbate, tocopherol, uric acid, serum albumin and glutathione can reduce profluorescent nitroxides to the hydroxylamines, resulting in the recovery of fluorescence (see Chapter 2). However, the main disadvantage of these probes is that the resulting hydroxylamine can be reoxidized to nitroxide radical by oxygen in the air, as shown in **Scheme 4.45**. This can potentially causes false results in the detection of reducing agent, or underestimation of the amount of reducing agent. The goal of this project was to design a profluorescent nitroxide sensor of mild reductants which undergoes cyclization upon formation of the hydroxylamine as shown in **Scheme 4.45**. Unlike

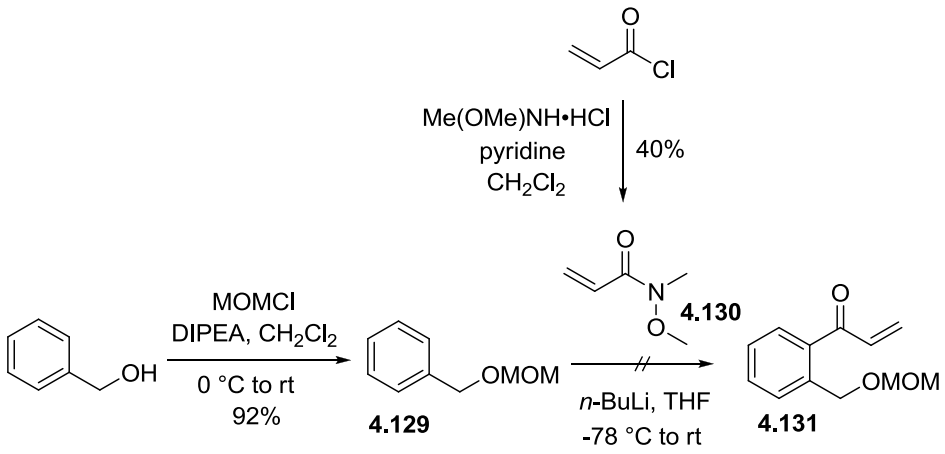
existing methodologies, this sensor is non-reversible, since it cannot be reoxidized in the presence of oxygen.



Scheme 4.45 General profluorescent nitroxide: the hydroxylamines can be reoxidized to nitroxide; and designed profluorescent nitroxides which undergo cyclization upon formation of the hydroxylamine

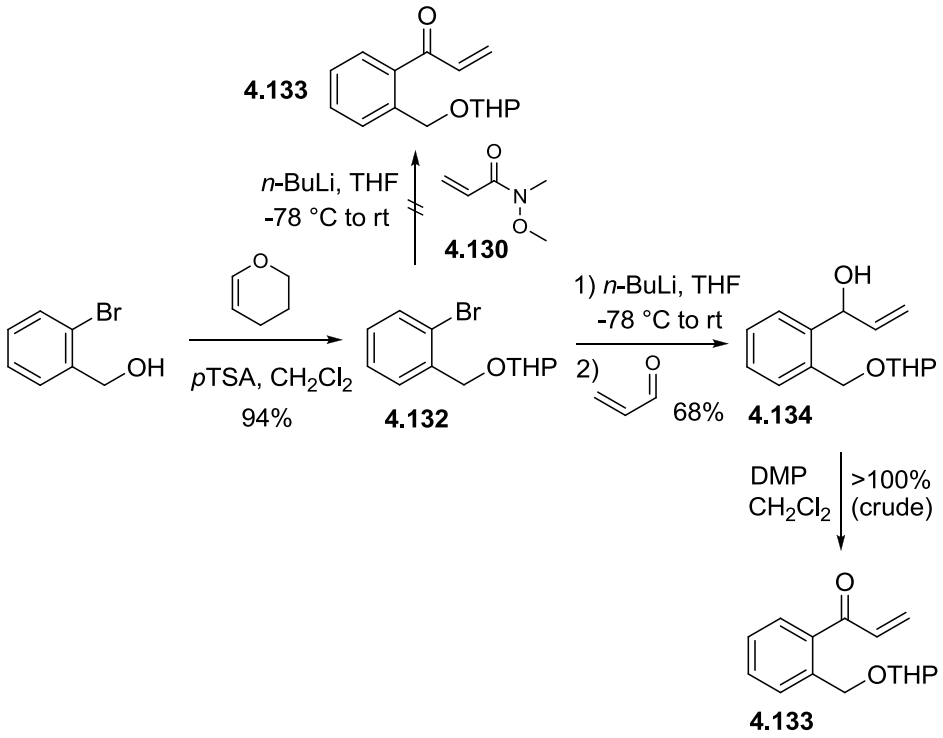
The synthesis of a profluorescent nitroxide for detection of reducing agents began with the protection of benzyl alcohol by substitution of methyl chloromethyl

ether (MOMCl) in the presence of DIPEA to give benzyl methoxymethyl ether **4.129** in 92% yield (**Scheme 4.46**). The use of the MOM-protected benzyl alcohol was hoped to assist in ortho lithiation in the same manner as seen with MOM-protected phenol.[72] However lithiation of **4.129** with *n*-BuLi, followed by addition to Weinreb amide **4.130**, prepared from acryloyl chloride and *N*,*O*-dimethylhydroxylamine hydrochloride, did not afford the desired product **4.131**. Addition of tetramethylethylenediamine (TMEDA) still gave only recovery of starting materials. Mocci *et al*.[73] reported that the metalation reaction of benzyl methoxymethyl ether **4.129** with *n*-BuLi or *sec*-BuLi occurred regioselectively at the benzylic position, with no evidences of substitution on the aromatic ring.



Scheme 4.46 Synthesis of benzyl methoxymethyl ether **4.129**, and attempt to carry out ortho lithiation, followed by nucleophilic substitution to Weinreb amide **4.130**

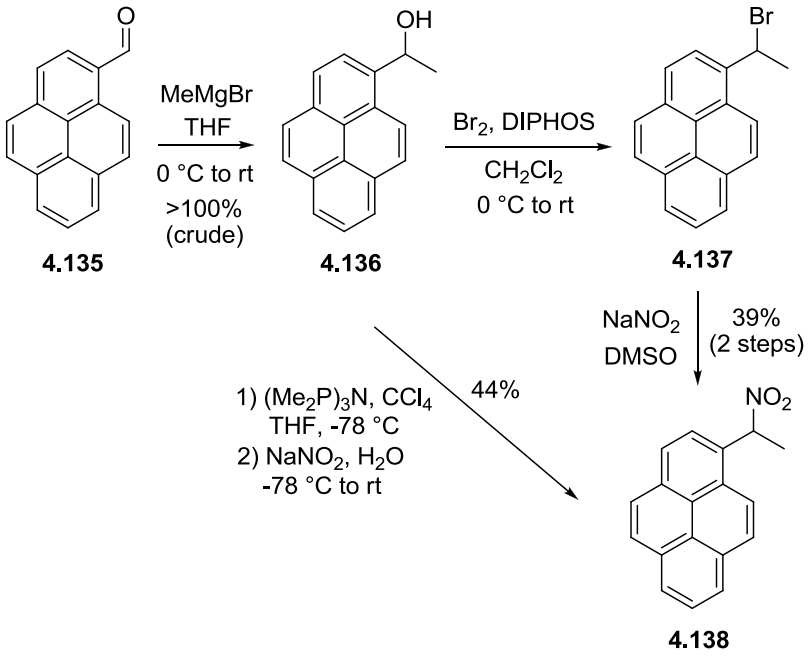
A new approach to functionalize the aromatic ring was lithium-halogen exchange at the ortho position of the benzyl alcohol. 2-Bromobenzyl alcohol was protected with the THP group to afford 2-(2-bromobenzyloxy)tetrahydro-2H-pyran **4.132** in 94% yield. Lithium exchange between *n*-BuLi and **4.132**, followed by addition to Weinreb amide **4.130** failed to give the desired ketone **4.133** (**Scheme 4.47**). Instead, addition of the lithiated species from **4.132** to acrolein gave two diastereomers of allylic alcohol **4.134** in 68% yield. Subsequent oxidation of **4.144** using Dess-Martin periodinane (DMP) provided unsaturated ketone **4.135** in >100% crude yield. When ketone **4.135** was purified by column chromatography, polymerization occurred, resulting in only 20% yield of the product. As a consequence, ketone **4.133** was used in the next reaction without purification, and stored in the presence of hydroquinone to prevent free radical polymerization.



Scheme 4.47 Synthesis of α,β-unsaturated ketone **4.133** from 2-bromobenzyl alcohol

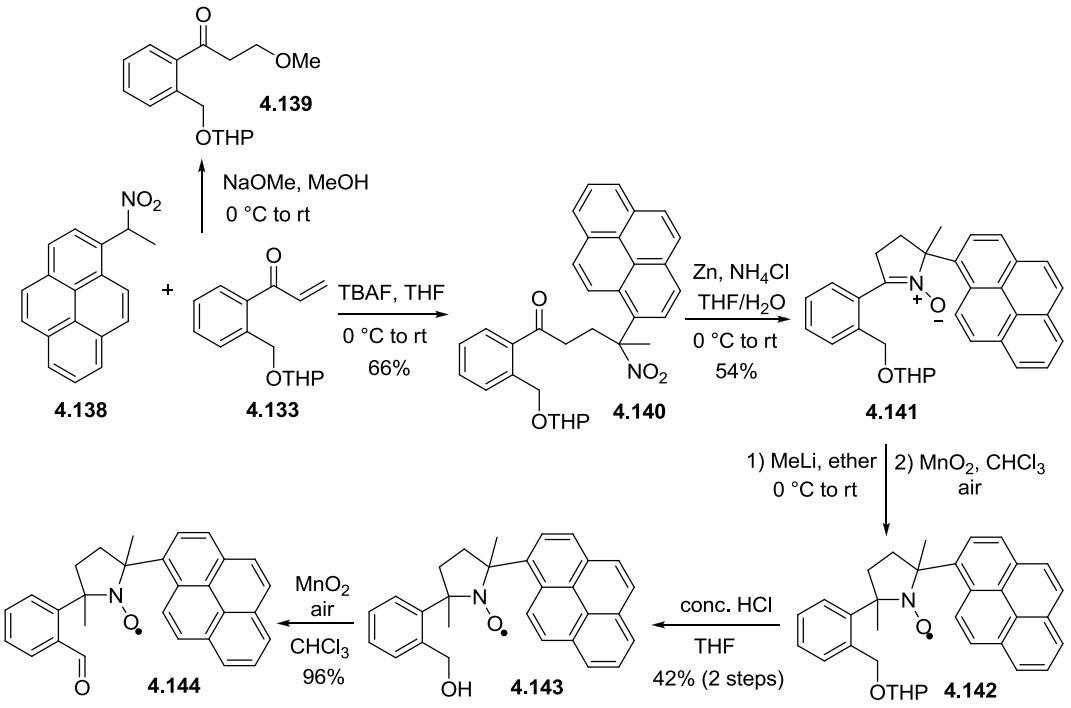
To introduce a fluorophore onto the nitroxide skeleton, pyrene was selected. Thus, 1-(1-nitroethyl)pyrene **4.138** was prepared from 1-pyrenecarboxaldehyde **4.135** (**Scheme 4.48**). Addition of methyl Grignard to 1-pyrenecarboxaldehyde **4.135** afforded 1-(pyren-1-yl)ethanol **4.136** in >100% crude yield. Following the procedure of Schmidt and Brooks,[74] the sensitive secondary benzylic alcohol **4.136** was converted to the bromide **4.137** by treatment with 1,2-bis(diphenylphosphino)ethane (DIPHOS) and liquid bromine. This delicate secondary bromide **4.137** was obtained after precipitation of diphosphine oxide by-product in a

0.5:1:2 ratio of dichloromethane:ether:pentane, followed by simple filtration. 1-(1-Nitroethyl)pyrene **4.138** was prepared in 39% yield (over two steps) by substitution of the bromide **4.137** with sodium nitrite.[36] This synthetic route was intermittently non-reproducible, presumably due to the instability of the secondary bromide **4.137**, which is prone to elimination. An alternative route converted alcohol **4.136** directly to the nitropyrene **4.138** in 44% yield using hexamethylphosphorus triamide (HMPT), carbon tetrachloride and sodium nitrite.



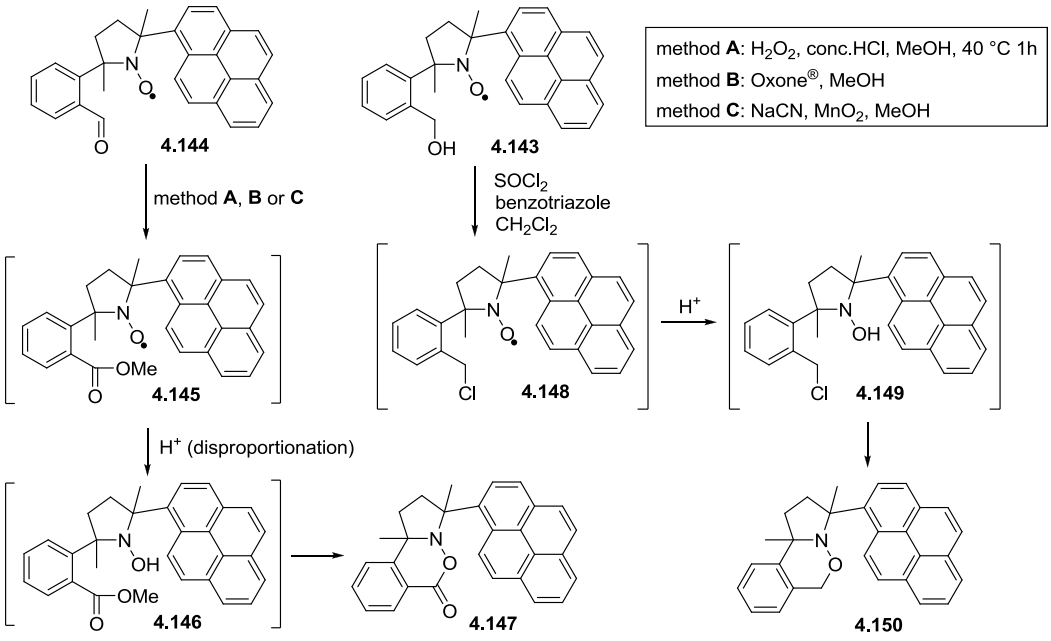
Scheme 4.48 Synthesis of nitro pyrene **4.138** from 1-pyrenecarboxaldehyde **4.135**

An attempt to effect Michael addition of the anion of nitropyrene **4.138** to unsaturated ketone **4.133** using sodium methoxide as a base was unsuccessful. Instead, only the undesired product **4.139**, resulting from Michael addition of methoxide to unsaturated ketone **4.133** (**Scheme 4.49**) was obtained. Use of TBAF as the base provided the desired product **4.140** in 66% yield. Nitropyrenes **4.138** and **4.140** are not fluorescent, presumably due to quenching from the oxygen lone pair of the nitro group. Reduction of nitropyrene **4.140** with zinc and ammonium chloride, followed by cyclization afforded fluorescent nitrone **4.141** in 54% yield. Addition of methyl lithium, following by oxidation provided two diastereomers of profluorescent nitroxide **4.142**. The THP group of **4.142** was then deprotected with hydrochloric acid to give benzyl alcohol **4.143** in 42% yield over two steps. Deprotection of the THP group with *p*TSA was unsuccessful. Oxidation of the benzyl alcohol **4.143** with manganese dioxide and air provided aldehyde **4.144** in 96% yield.



Scheme 4.49 Synthesis of aldehyde **4.144** from nitropyrene **4.138** and unsaturated ketone **4.133**

Multiple attempts to carry out one-pot oxidation and esterification of aldehyde **4.144** included the use of hydrogen peroxide, hydrochloric acid and methanol,[75] Oxone® and methanol,[76] and sodium cyanide, manganese dioxide and methanol (the Corey-Gilman-Ganem oxidation) (**Scheme 4.50**).[77] All of these conditions did not provide the desired product **4.145**, but instead formed cyclic ester **4.147**. Under the first two conditions, it is assumed that nitroxide disproportionates under the acidic conditions to give hydroxylamine **4.146**, which then cyclized to afford cyclic ester **4.147**. Oxidation of the alcohol **4.143** directly to ester **4.145** in



Scheme 4.50 Attempts to convert aldehyde **4.144** to ester **4.145**, and benzyl alcohol **4.143** to the benzyl chloride **4.148**

methanol was also unsuccessful.[78] A revised strategy was chosen, to convert the alcohol into a good leaving group, such as chloride. Use of thionyl chloride and benzotriazole[79] was unsuccessful in producing the benzyl chloride **4.148**; instead cyclic ether **4.150** was formed, presumably though hydroxylamine **4.149** (**Scheme 4.50**). Again, it was assumed that failure of the reaction is due to slightly acidic conditions, even though excess benzotriazole was added. The next plan is to use triphenyl phosphine and carbon tetrachloride to give the desired benzyl chloride **4.148**.[80]

4.7 Conclusion

Two synthetic approaches to prepare nitroxides bearing tethered photocleavable side groups were developed. Nitroxides with appended photosensitive dithiocarbamate esters were synthesized from coupling reactions of carboxylic acids and dithiocarbamate **4.20**. Photolysis of dithiocarbamate nitroxide **4.58** provided a volatile alkoxyamine product which was lost *in vacuo*. Upon irradiation, dithiocarbamate nitroxide **4.67** with a phenyl group substituted on the nitroxide pyrrolidine ring successfully trapped the transient radical intramolecularly to form cyclic *N*-alkoxylamine **4.68**. Anthracene dye was tethered to the nitroxide via click chemistry to form dithiocarbamate profluorescent nitroxide **4.87**. The fluorescence which was originally quenched by the nitroxide was restored upon photoexcitation and cyclization. The azide/alkyne cycloaddition provides a general method to introduce fluorophores. Assisted by the proximal carboxylic acid, alkynyl nitroxide **4.82** can be "clicked" with a variety of azido fluorophores, which will be useful for site-specific labeling of complex biological systems or materials by localized laser excitation.

The synthesis of nitroxides bearing a side group designed for Norrish type I cleavage was explored. However, photo-irradiation of nitroxide **4.120** bearing a benzyl ketone did not afford the desired carbon radical-trapped product. It is assumed that the nitroxide radical quenches the excited triplet state of the ketone,

and thus prevents Norrish type I cleavage. Instead it appears that nitroxide **4.120** was photo-reduced, followed by cyclization to form the acetal **4.125**.

A profluorescent nitroxide sensor of mild reducing agents was developed, which undergoes cyclization upon formation of the hydroxylamine. This sensor will be non-reversible, since it cannot be reoxidized in the presence of oxygen. Attempts to convert the benzyl alcohol of profluorescent nitroxide **4.143** to ester **4.145** or benzyl chloride **4.148** were unsuccessful, presumably due to disproportionation of nitroxide under the slightly acidic reaction conditions. Conversion of benzyl alcohol **4.143** to benzyl chloride **4.148** under non-acidic conditions using triphenylphosphine and carbon tetrachloride is being pursued.

4.8 References

1. Zard, S. Z., *Angewandte Chemie-International Edition in English* **1997,** *36* (7), 673-685.

2. Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Journal of the Chemical Society-Chemical Communications* **1983,** (17), 939-941; Barton, D. H. R.; Crich, D.; Potier, P., *Tetrahedron Letters* **1985,** *26* (48), 5943-5946.

3. Newcomb, M.; Deeb, T. M.; Marquardt, D. J., *Tetrahedron* **1990,** *46* (7), 2317-2328; Esker, J. L.; Newcomb, M., *Tetrahedron Letters* **1992,** *33* (40), 5913-5916.

4. Newcomb, M.; Kumar, M. U.; Boivin, J.; Crepon, E.; Zard, S. Z., *Tetrahedron Letters* **1991,** *32* (1), 45-48; Newcomb, M.; Dhanabalasingam, B., *Tetrahedron Letters* **1994,** *35* (29), 5193-5196.

5. Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Tetrahedron* **1985,** *41* (19), 3901-3924.

6. Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A., *Tetrahedron* **1992,** *48* (13), 2613-2626.

7. Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Tetrahedron Letters* **1983,** *24* (45), 4979-4982; Barton, D. H. R.; Lacher, B.; Zard, S. Z., *Tetrahedron Letters* **1985,** *26* (48), 5939-5942; Barton, D. H. R.; Ozbalik, N.; Vacher, B., *Tetrahedron* **1988,** *44* (12), 3501-3512.

8. Kim, S.; Lee, I. Y.; Yoon, J. Y.; Oh, D. H., *Journal of the American Chemical Society* **1996,** *118* (21), 5138-5139.

9. Hay, B. P.; Beckwith, A. L. J., *Journal of Organic Chemistry* **1989,** *54* (18), 4330-4334.

10. Barton, D. H. R.; Crich, D.; Kretzschmar, G., *Journal of the Chemical Society-Perkin Transactions 1* **1986,** (1), 39-53; Hartung, J., *Synlett* **1996,** (12), 1206-1208; Hartung, J.; Schwarz, M., *Synlett* **1997,** (7), 848-850.

11. Kim, S.; Lim, C. J.; Song, S. E.; Kang, H. Y., *Synlett* **2001,** (5), 688-690.

12. Kim, S.; Lim, C. J.; Song, S. E.; Kang, H. Y., *Chemical Communications* **2001,** (15), 1410-1411.

13. Lee, S.; Lim, C. J.; Kim, S., *Bulletin of the Korean Chemical Society* **2004,** *25* (11), 1611-1612.

14. Cho, C. H.; Kim, S., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2005,** *83* (6-7), 917-921.

15. Fenner, T.; Schiesser, C. H., *Molecules* **2004,** *9* (6), 472-479; Fenner, T.; White, J. M.; Schiesser, C. H., *Organic & Biomolecular Chemistry* **2006,** *4* (3), 466-474.

16. Carland, M. W.; Martin, R. L.; Schiesser, C. H., *Organic & Biomolecular Chemistry* **2004,** *2* (18), 2612-2618.

17. Nyfeler, E.; Renaud, P., *Organic Letters* **2008,** *10* (5), 985-988.

18. Klan, P.; Wirz, J., *Photochemistry of Organic Compounds: From Concepts to Practice*. John Wiley & Sons Ltd: West Sussex, 2009.

19. Robbins, W. K.; Eastman, R. H., *Journal of the American Chemical Society* **1970,** *92* (20), 6077-6079.

20. Skene, W. G.; Scaiano, J. C.; Listigovers, N. A.; Kazmaier, P. M.; Georges, M. K., *Macromolecules* **2000,** *33* (14), 5065-5072.

21. Ananchenko, G. S.; Fischer, H., *Journal of Polymer Science Part a-Polymer Chemistry* **2001,** *39* (20), 3604-3621.

22. Coenjarts, C.; Garcia, O.; Llauger, L.; Palfreyman, J.; Vinette, A. L.; Scaiano, J. C., *Journal of the American Chemical Society* **2003,** *125* (3), 620-621.

23. Aspee, A.; Maretti, L.; Scaiano, J. C., *Photochemical & Photobiological Sciences* **2003,** *2* (11), 1125-1129.

24. Meyers, A. I.; Temple, D. L.; Haidukew.D; Mihelich, E. D., *Journal of Organic Chemistry* **1974,** *39* (18), 2787-2793.

25. Michon, P.; Rassat, A., *Journal of Organic Chemistry* **1974,** *39* (14), 2121-2124.

26. Huang, P. Q.; Zheng, X.; Deng, X. M., *Tetrahedron Letters* **2001,** *42* (51), 9039-9041.

27. Gomtsyan, A., *Organic Letters* **2000,** *2* (1), 11-13.

28. Zhao, M. Z.; Li, J.; Mano, E.; Song, Z. G.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J., *Journal of Organic Chemistry* **1999,** *64* (7), 2564-2566.

29. Noyori, R.; Aoki, M.; Sato, K., *Chemical Communications* **2003,** (16), 1977-1986.

30. Hunsen, M., *Synthesis-Stuttgart* **2005,** (15), 2487-2490.

31. Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K., *Organic Letters* **2005,** *7* (14), 2933-2936.

32. Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocienski, P.; Pimm, A.; Bell, R., *Synthesis-Stuttgart* **1995,** (2), 199-206.

33. Mazitschek, R.; Mulbaier, M.; Giannis, A., *Angewandte Chemie-International Edition* **2002,** *41* (21), 4059-4061.

34. Dalcanale, E.; Montanari, F., *Journal of Organic Chemistry* **1986,** *51* (4), 567-569.

35. Lilie, E. The Development of Fluorescent Nitroxide Probing Systems: Synthetic Progress Toward a Profluorescent Nitroxide Probe for Urushiol and Examination of Binding and Quenching in Nitroxide–CdSe Quantum Dot Complexes. Thesis (B.Sc.), University of California, Santa Cruz, 2009.

36. Kornblum, N.; Wade, P. A., *Journal of Organic Chemistry* **1973,** *38* (7), 1418-1420.

37. Sar, C. P.; Jeko, J.; Fajer, P.; Hideg, K., *Synthesis-Stuttgart* **1999,** (6), 1039-1045.

38. Keddie, D. J.; Fairfull-Smith, K. E.; Bottle, S. E., *Organic & Biomolecular Chemistry* **2008,** *6* (17), 3135-3143.

39. Fairfull-Smith, K. E.; Bottle, S. E., *European Journal of Organic Chemistry* **2008,** (32), 5391-5400.

40. Baracz, N. M.; Hankovszky, O. H.; Sar, C. P.; Jerkovich, G.; Hideg, K., *Synthesis-Stuttgart* **1996,** (2), 204-208.

41. Hernandez, E.; Soderquist, J. A., *Organic Letters* **2005,** *7* (24), 5397-5400.

42. Morris, J. C.; McMurtrie, J. C.; Bottle, S. E.; Fairfull-Smith, K. E., *Journal of Organic Chemistry* **2011,** *76* (12), 4964-4972.

43. Acharya, H. P.; Miyoshi, K.; Kobayashi, Y., *Organic Letters* **2007,** *9* (18), 3535-3538.

44. Karade, N. N.; Tiwari, G. B.; Huple, D. B., *Synlett* **2005,** (13), 2039-2042.

45. Singh, A. K.; Varma, R. S., *Tetrahedron Letters* **1992,** *33* (17), 2307-2310.

46. Ruggeri, S. G.; Bill, D. R.; Bourassa, D. E.; Castaldi, M. J.; Houck, T. L.; Ripin, D. H. B.; Wei, L. L.; Weston, N., *Organic Process Research & Development* **2003,** *7* (6), 1043-1047.

47. Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q., *Organic Letters* **2004,** *6* (24), 4603-4606.

48. Kuang, G. C.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Zhu, L., *Journal of Organic Chemistry* **2010,** *75* (19), 6540-6548.

49. Eames, J.; Coumbarides, G. S.; Suggate, M. J.; Weerasooriya, N., *European Journal of Organic Chemistry* **2003,** (4), 634-641.

50. Kawai, M.; Onaka, M.; Izumi, Y., *Journal of the Chemical Society-Chemical Communications* **1987,** (15), 1203-1204.

51. Loh, T. P.; Li, X. R., *Tetrahedron* **1999,** *55* (35), 10789-10802.

52. Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G., *Australian Journal of Chemistry* **1990,** *43* (12), 2045-2062.

53. Shimoyama, I.; Zhang, Y. T.; Wu, G. Z.; Negishi, E., *Tetrahedron Letters* **1990,** *31* (20), 2841-2844.

54. Schlosser, M.; Brich, Z., *Helvetica Chimica Acta* **1978,** *61* (5), 1903-1911.

55. Stork, G.; Franklin, P. J., *Australian Journal of Chemistry* **1992,** *45* (1), 275-284.

56. Gadanyi, S.; Kalai, T.; Jeko, J.; Berente, Z.; Hideg, K., *Synthesis-Stuttgart* **2000,** (14), 2039-2046.

57. Pahari, P.; Rohr, J., *Journal of Organic Chemistry* **2009,** *74* (7), 2750-2754.

58. Haire, D. L.; Hilborn, J. W.; Janzen, E. G., *Journal of Organic Chemistry* **1986,** *51* (22), 4298-4300.

59. Bapat, J. B.; Black, D. S. C., *Australian Journal of Chemistry* **1968,** *21* (10), 2483-2495.

60. Muratake, H.; Natsume, M.; Nakai, H., *Tetrahedron* **2004,** *60* (51), 11783-11803; Li, S. L.; Chiu, P., *Tetrahedron Letters* **2008,** *49* (11), 1741-1744.

61. Therkelsen, F. D.; Hansen, A. L. L.; Pedersen, E. B.; Nielsen, C., *Organic & Biomolecular Chemistry* **2003,** *1* (16), 2908-2918; Moorthy, J. N.; Samanta, S.; Koner, A. L.; Saha, S.; Nau, W. M., *Journal of the American Chemical Society* **2008,** *130* (41), 13608-13617.

62. Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J., *Journal of Organic Chemistry* **2005,** *70* (23), 9430-9435.

63. Prakesch, M.; Gree, D.; Gree, R., *Tetrahedron* **2003,** *59* (44), 8833-8841.

64. Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C., *Journal of the American Chemical Society* **2005,** *127* (19), 6970-6971.

65. Detsi, A.; Roussis, V.; Tsotinis, A.; Roussakis, C.; Calogeropoulou, T., *Synlett* **2005,** (20), 3131-3135.

66. Tang, J. M.; Bhunia, S.; Sohel, S. M. A.; Lin, M. Y.; Liao, H. Y.; Datta, S.; Das, A.; Liu, R. S., *Journal of the American Chemical Society* **2007,** *129* (50), 15677-15683.

67. Riahi, A.; Henin, F.; Muzart, J., *Tetrahedron Letters* **1999,** *40* (12), 2303-2306.

68. Sani-Souna-Sido, A.; Chassaing, S.; Pale, P.; Sommer, J., *Applied Catalysis A-General* **2008,** *336* (1-2), 101-108.

69. Hong, W. P.; Lee, K. J., *Synthesis-Stuttgart* **2006,** (6), 963-968.

70. Liang, G. X.; Xu, Y.; Seiple, I. B.; Trauner, D., *Journal of the American Chemical Society* **2006,** *128* (34), 11022-11023.

71. Liu, H. J.; Feng, W.; Kee, C. W.; Zhao, Y. J.; Leow, D.; Pan, Y. H.; Tan, C. H., *Green Chemistry* **2010,** *12* (6), 953-956.

72. Winkle, M. R.; Ronald, R. C., *Journal of Organic Chemistry* **1982,** *47* (11), 2101-2108.

73. Azzena, U.; Pisano, L.; Mocci, S., *Journal of Organometallic Chemistry* **2009,** *694* (22), 3619-3625.

74. Schmidt, S. P.; Brooks, D. W., *Tetrahedron Letters* **1987,** *28* (7), 767-768.

75. Takeda, T.; Watanabe, H.; Kitahara, T., *Synlett* **1997,** (10), 1149-1150.

76. Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B., *Organic Letters* **2003,** *5* (7), 1031-1034.

77. Lai, G. F.; Anderson, W. K., *Synthetic Communications* **1997,** *27* (7), 1281-1283.

78. Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K., *Synthesis-Stuttgart* **2003,** (7), 1055-1064.

79. Chaudhari, S. S.; Akamanchi, K. G., *Synlett* **1999,** (11), 1763-1765.

80. Genrich, F.; Schaumann, E., *Tetrahedron Letters* **2009,** *50* (45), 6187-6190; Liu, H.; Dong, A.; Gao, C.; Tan, C.; Liu, H.; Zu, X.; Jiang, Y., *Bioorganic & Medicinal Chemistry* **2008,** *16* (23), 10013-10021.

Chapter 5: Thiol Chain-End Functionalized Polymers Prepared by Nitroxide Mediated Polymerization for Quantum Dot Encapsulation

5.1 Introduction

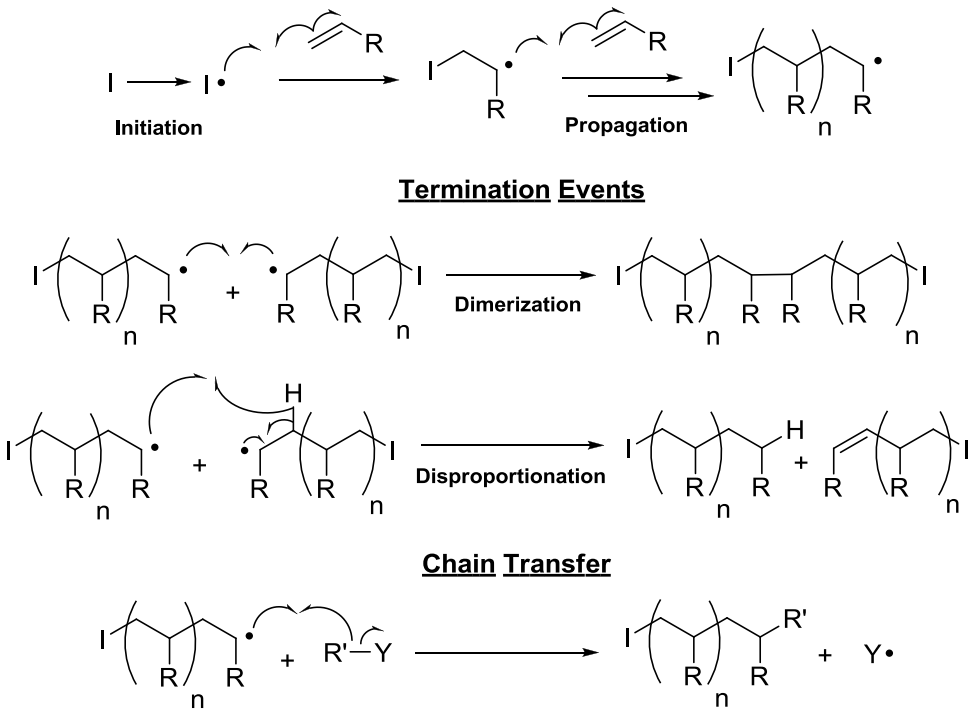
Quantum dots (QDs) are semiconductor nanoparticles that exhibit unique fluorescent properties, but have a tendency to associate because of their large surface-to-volume ratio. To overcome this problem, various strategies of nanoparticle preparation and size control have been investigated. These include encapsulation in sol-gels,[1] in polymer matrixes, and the use of organic capping agents (*vide infra*). Current synthetic methods result in a tri-*n*-octylphosphine oxide (TOPO) coating around the dots; however polymers provide several advantages over small-molecule ligands.[2] Polymers consist of multiple repeating units, resulting in a much greater degree of multivalency. Moreover, the thickness of the stabilizing layers on the nanoparticle surface can be controlled through adjustment of the length of the polymers. As ligand molecular weight increases, the rate of dissociation from the nanoparticle surface decreases due to greater protection from oxidation and aggregation. In addition, inorganic-organic hybrid materials that combine the unique properties of quantum-confined particles with that of polymers are interesting candidates for combining the two desired properties in a synergistic way. Polymers can provide QDs with various properties such as solubility in different

solvents and film formation. In order to use quantum dots as fluorescent tags in most biological applications, they must be soluble in water. Copolymers allow for the incorporation of multiple types of ligand functionality, and a hydrophilic block allows quantum dots to dissolve in aqueous solution. Living free radical polymerization (LFRP) has emerged as a powerful tool for manipulating the size, shape, and functionality of polymers on the molecular level; therefore it is suitable to design polymer coatings for QDs.

5.2 Living Free Radical Polymerization (LFRP) and Nitroxide Mediated Radical Polymerization (NMRP)

Conventional radical polymerization is an uncontrolled chain reaction: initiation, propagation and termination[3] are shown in **Scheme 5.1**. Due to significant termination (dimerization and disproportionation) or chain transfer, the resulting polymer displays poor molecular weight control and undefined chain ends.

In contrast to conventional polymerization, LFRP is used to synthesize polymers with controlled molecular weights and low polydispersities. The term "living" is used to describe a class of chain-growth polymerizations which react in a controlled manner until manually terminated.[4] Generally, a living polymerization is defined by three characteristics: the ability to predict molecular weight of the polymer based on initiator concentration and polymerization time, low



Scheme 5.1 Traditional polymerization begins with initiation followed by propagation. Chain growth is terminated through two processes: dimerization and disproportionation or by chain transfer.

polydispersity, and the resultant polymer can function as a macroinitiator to effect subsequent polymerization.

The measure of the molecular weight distribution is the polydispersity index (PDI), which is expressed as the ratio of the weight average molecular weight (M_w) and the number average molecular weight (M_n) (**equation 5.1**).

$$\boldsymbol{PDI = \frac{M_w}{M_n}} \qquad \textbf{equation 5.1}$$

If polymers are of uniform chain length, the PDI equals 1.0. The accepted PDI for a "controlled polymerization" is 1.5 or lower. PDI and polymer molecular weight can be determined by high performance liquid chromatography (HPLC) known as gel permeation chromatography (GPC) or size exclusion chromatography (SEC), which utilizes a series of columns packed with materials of different pore sizes. Larger polymer chains pass through the column faster than smaller chains, as smaller polymers are trapped in the porous material. A refractive index or UV-visible detector measures the signal as polymers are eluted. The affiliated software compares the data with polymer standards of known molecular weight to provide M_n, M_w, and PDI.

The monomer conversion is determined by analysis of the crude polymerization mixture using ^1H nuclear magnetic resonance (NMR). Monomers which are incorporated into the polymer give broad signals, while unconsumed monomers give sharp signals. The percent conversion is calculated by integrating polymer peaks versus remaining monomer peaks. Gravimetric analysis is another technique for determining monomer conversion. It is achieved by comparing the experimental mass of the polymer isolated to the theoretical amount that could be obtained.

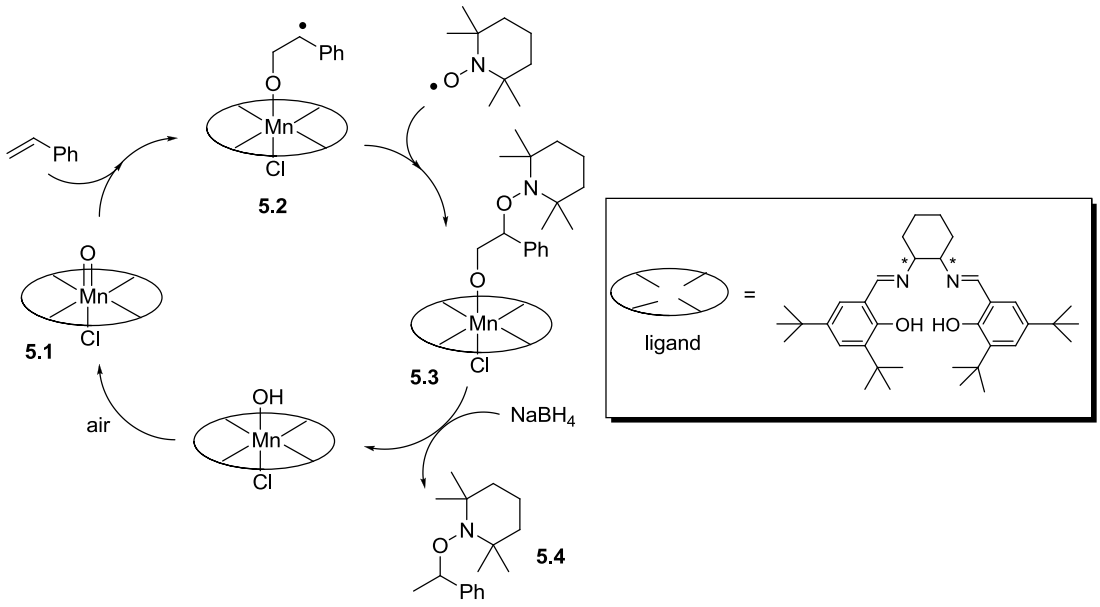
A variety of macromolecular structures including block, random, and gradient copolymers can be constructed through living polymerization. The use of designed

unimolecular initiators has allowed the preparation of advanced polymers, including materials with novel molecular architectures such as comb, star, and dendritic topologies. Selective functionalization of polymers is also possible, and can be utilized to conjugate the polymers to surfaces, quantum dots, and biomolecules. In terms of material properties, LFRP can be used to polymerize a wide range of monomers, since radicals are chemoselective and do not react with functionalized groups such as esters, amides and nitriles found on acrylates, acrylamides, and acrylonitriles. However, radical polymerization is still susceptible to reaction with molecular oxygen, thus reaction vessels must be deoxygenated prior to polymerization.

Three common types of LFRP are atom transfer radical polymerization (ATRP), reversible addition fragmentation transfer (RAFT), and nitroxide mediated radical polymerization (NMRP). In the Braslau laboratory, research is focused on NMRP.[5] IUPAC has recently recommended the use of “reversible-deactivation radical polymerization” (RDRP) instead of the more widely used “living/controlled free radical polymerization” (LFRP), since termination by radical-radical reactions or chain transfer reactions will always occur, no matter how minimal the termination might be within radical polymerization systems.[6] The term “nitroxide” is also discouraged in IUPAC nomenclature. Thus “nitroxide-mediated radical polymerization” (NMRP) should be called “aminoxyl-mediated radical polymerization” (AMRP) following

IUPAC conventions. However, the predominant and common usage of "nitroxide" and "NMRP" will be utilized in this thesis.

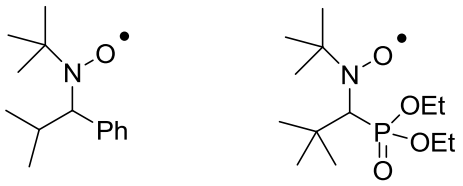
NMRP originated from the work of Solomon, Rizzardo, and Moad which utilized the persistent radical 2,2,6,6-tetramethylpiperidioxyl (TEMPO) as a radical trap in free radical polymerization to investigate the initiation mechanism.[7,8] However, this method failed to produce polymers with narrow molecular weight distributions. Afterwards, Georges *et al*., introduced the first examples of controlled styrene polymerization initiated with benzoyl peroxide (BPO) or azobisisobutyronitrile (AIBN) mediated with TEMPO.[9] These polymerizations produced polystyrene with controlled molecular weights and low polydispersities. In 1994 the Hawker research group improved this work, simplifying the nitroxide-mediated radical polymerization by preparation of TEMPO-based *N*-alkoxyamines as unimolecular initiator/mediators. He later introduced Jacobsen's manganese catalyst as a convenient method to prepared these *N*-alkoxyamines (**Scheme 5.2**).[10] During the Jacobsen epoxidation of styrene, the manganese complex **5.1** generates a carbon centered radical intermediate **5.2**. This intermediate is trapped with a persistent nitroxide such as TEMPO to form *N*-alkoxyamine complex **5.3**. *N*-Alkoxyamine **5.4** is released and the manganese catalyst is reformed by reductive cleavage of C-O bond and subsequent oxidation of the manganese. TEMPO mediated polymerization has been reviewed.[11]



Scheme 5.2 Preparation of TEMPO-based *N*-alkoxyamines utilizing Jacobsen's manganese catalyst developed by Hawker *et al*.[10]

Although TEMPO and other cyclic nitroxides are successful in controlling the polymerization of styrene monomers, they do not control polymerizations of acrylate, acrylamide, or acrylonitrile monomers. To circumvent this problem, a new generation of acyclic nitroxides was developed, the most successful of which are 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO), which was introduced by Hawker and Braslau,[12] and *N*-*tert*-butyl-1-diethylphosphono-2,2-dimethylpropyl nitroxide (SG1), which was designed by Gnanou and Tordo (**Figure 5.1**).[13] These nitroxides bear a hydrogen α to the nitrogen, which provides a decomposition pathway not possible to TEMPO, resulting in a low concentration of free nitroxide during the polymerization process, and thus faster polymerization rates, and the

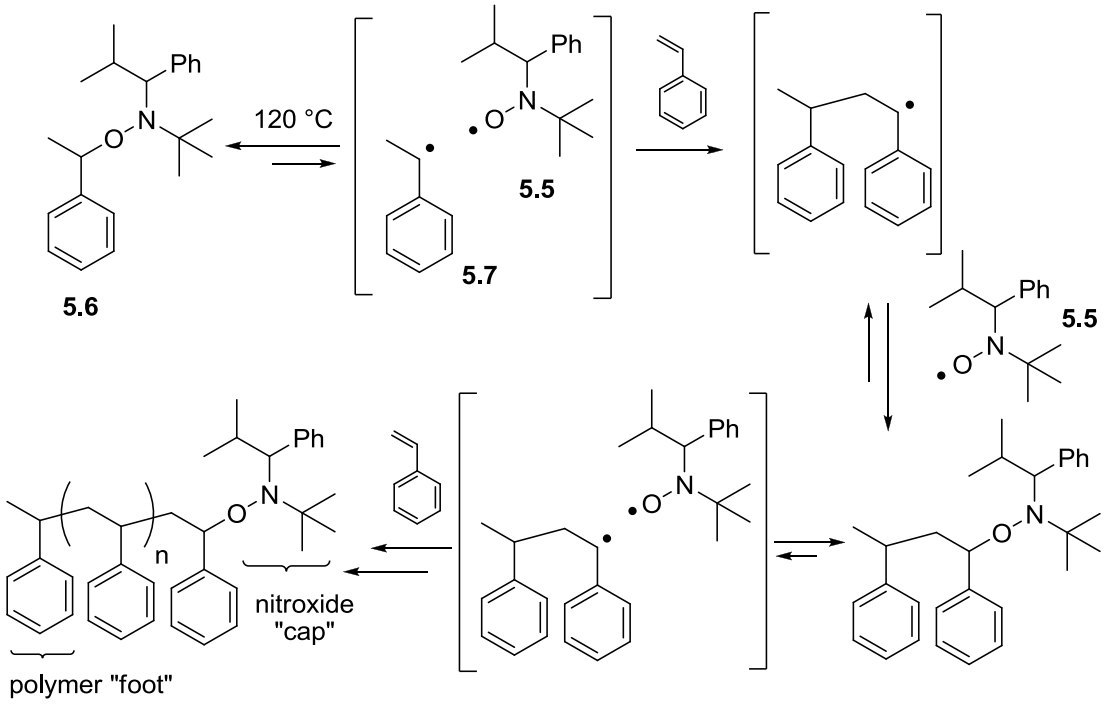
"livingness" of polymerization.[14] These α-H nitroxides have been used successfully in the controlled polymerizations of acrylates, acrylamides, dienes, and acrylonitriles. TIPNO **5.5** is commercially available from Aldrich, and SG1 from ARKEMA.



TIPNO 5.5 **SG1**

Figure 5.1 α-H Nitroxides commonly used in NMRP

The mechanism for radical polymerization of styrene using TIPNO-based initiator **5.6** is illustrated in **Scheme 5.3**. Upon heating at 120 °C, the C-O bond of alkoxyamine **5.6** homolytically cleaves to give the persistent nitroxide radical TIPNO **5.5** and a reactive phenethyl radical **5.7**. The phenethyl radical adds to styrene monomer; the newly formed radical is then reversibly trapped by TIPNO **5.5**. The new C-O bond undergoes the same homolytic cleavage, and adds subsequent monomers until all of the monomer is consumed, or the polymerization is stopped by removing the heat.



Scheme 5.3 Mechanism of nitroxide mediated radical polymerization (NMRP) of styrene using TIPNO-based initiator **5.5**

5.3 Quantum Dot Encapsulation by Thiolated Polymers

LFRP techniques provide access to polymers with defined and uniform structures bearing functional end-groups, which open the door to post-polymerization modification. End-functionalized polymers can be used in a variety of applications, from surface modification to the preparation of biomedical materials. Since the thiol group is a highly versatile functionality, thiolated polymers have attracted much attention. Sulfur can be incorporated into the polymer backbone, as substituents attached off the main chain,[15-17] or placed at the polymer termini.[18-22]

Thiols form strong bonds to a number of metal surfaces including gold[23-27] and silver.[28] Cadmium chalcogenide[29-31] nanoparticles, e.g. CdS,[32-34] CdSe,[35-38] CdTe,[39-43] are stabilized with covalently bound small thiol molecules. On capping with thiols, the weak sulfhydryl bond is replaced with a bond between sulfur and surface cadmium ions.[44] Thiolated polymers have also been applied on quantum dot surfaces (*vide infra*). Generally, polymer chains can be introduced onto quantum dots by two methods (**Figure 5.2**).[45] One is polymerization from the nanoparticle surface, called the "grafting-from" approach. For this purpose, a small ligand capable of subsequently triggering successive polymerization, such as RAFT,[46] nitroxide-mediated,[47] or ruthenium-catalyzed ring-opening metathesis (ROMP)[48] polymerization, is linked to the particle surface. It is also possible to anchor pre-formed polymers containing functional groups at the chain end by either ligand exchange or *in situ* formation.[2] This technique is known as the "grafting-to" approach (**Figure 5.2**). Polymer-nanoparticle composites can be formed by exchange

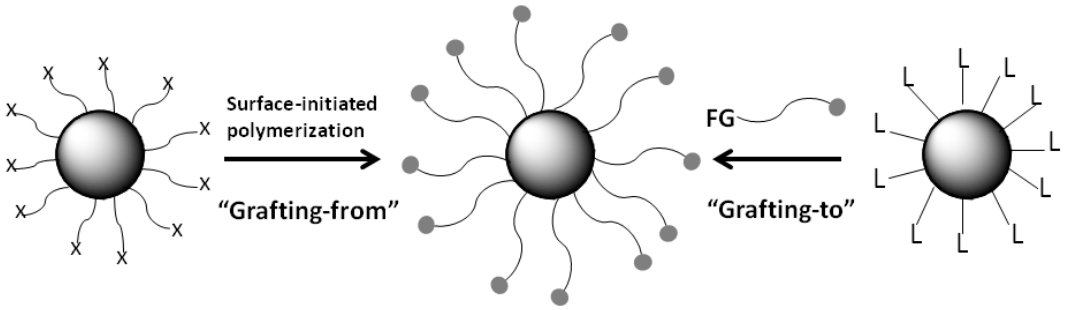


Figure 5.2 Schematic depiction of two methods for surface functionalization of nanoparticles with polymers (redrawn based on reference 45)

of small-molecule ligands on pre-formed nanoparticles with polymer ligands (**Figure 5.3a**). Alternatively, nanoparticles are synthesized in the presence of the polymer ligands (**Figure 5.3b**). This approach has the advantage that the polymer used for surface modification can be well characterized before grafting.

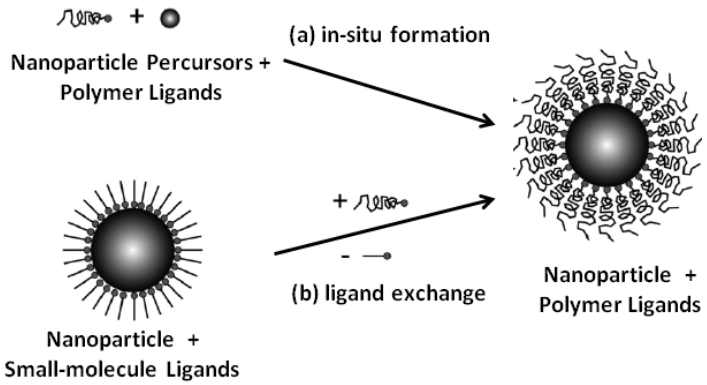
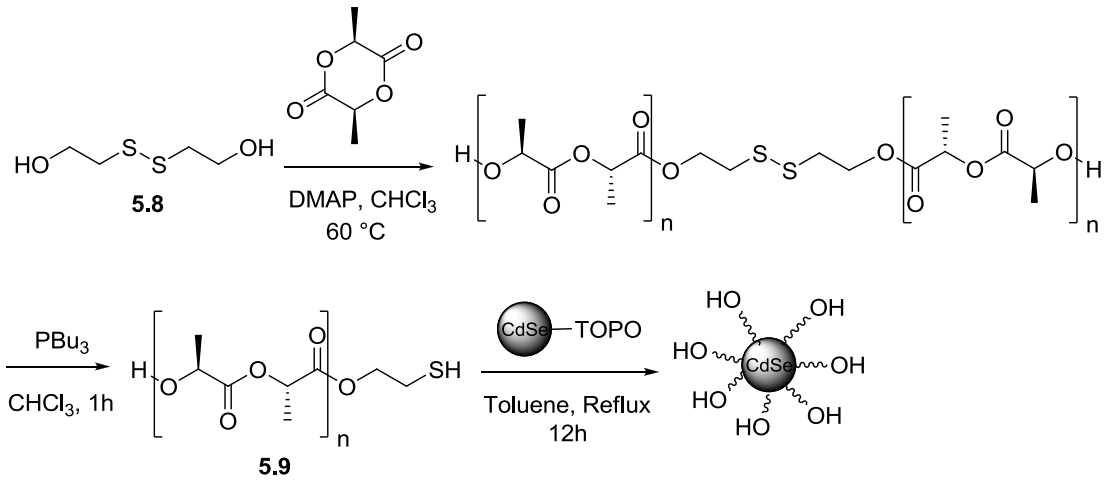


Figure 5.3 Schematic illustration of "grafting-to" approaches **(a)** in situ formation, and **(b)** ligand exchange for the preparation of polymer ligand-stabilized nanoparticles (redrawn based on reference 2)

The attachment of polymers to quantum dots using thiol functional groups has been demonstrated by a number of groups. Poly(L-lactide) disulfides were first prepared through the DMAP-catalyzed ring-opening polymerization of L-lactide with a dihydroxyethyl disulfide initiator **5.8**, and were reduced into thiol end-functionalized poly(L-lactide) **5.9** with tributyl phosphine (PBu_3).[49] Using a "grafting-to" approach, thiol chain-end polymers are exchanged with tri-*n*-octylphosphine oxide (TOPO) on QD surface to provide a biocompatible and biodegradable CdSe/polymer complex as shown in **Scheme 5.4**. The presence of free polymeric

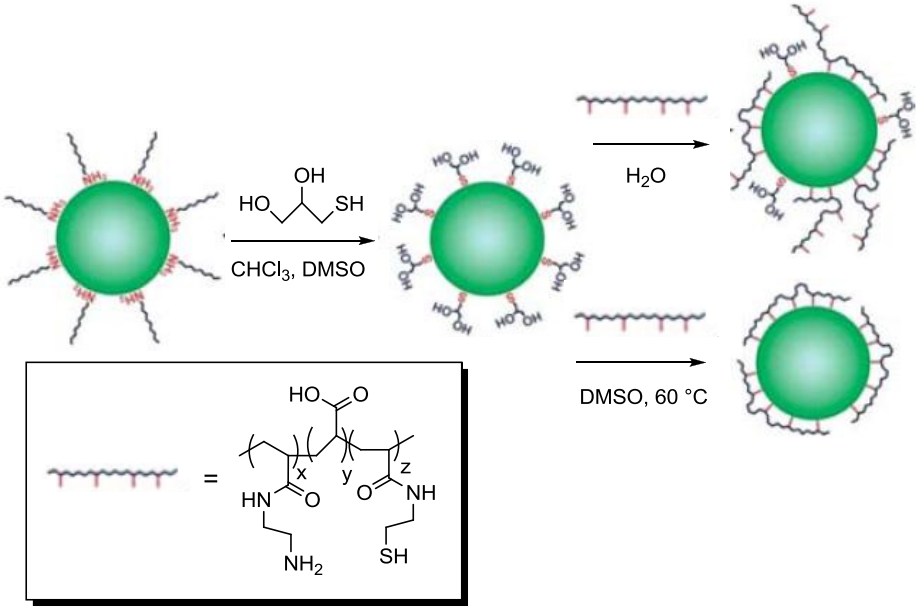
thiol ligands was found to be helpful for decreasing photochemical oxidation and enhancing the photoluminescence stability and quantum yield.



Scheme 5.4 Syntheis of thiol-end-functionalized poly(L-lactide) **5.9**, and attachment to form biodegradable core-shell CdSe/poly(L-lactide) quantum dots

Several thiol terminated,[50-53] or thiol side chained[54-56] polymers, as well as dendrimers[57, 58] have been synthesized and utilized in encapsulation of CdSe or CdS QDs to make them water soluble and biocompatible for labeling applications. A major problem in using QDs as a fluorescent probe is the large size of conventional QDs, which affects their molecular binding and *in vivo* biodistribution, preventing implementation of many QDs for biomedical imaging. This bulkiness is not an intrinsic problem of QD nanocrystals, but arises mainly from the organic surface coatings used for encapsulation and stabilization. In order to minimize the hydrodynamic size of QDs, multidentate polymer ligands such as copolymers

containing thiol groups in combination with amine or carboxylic groups pendant from the backbone are used to provide a dense, compact and hydrophilic covering on the surface of the CdSe[59] or CdTe[60] QDs. These multidentate polymers are also an effective barrier against solvent molecules, preventing them from coming into contact with the QD surface, and accordingly result in high chemical and colloidal stability of the QDs. As shown in **Scheme 5.5**, an alkylamine coat on CdTe QDs were first exchanged with hydrophilic thioglycerol in chloroform, due to the insolubility of the multidentate thiol/amine/carboxylic acid bearing polymer in nonpolar solvents.

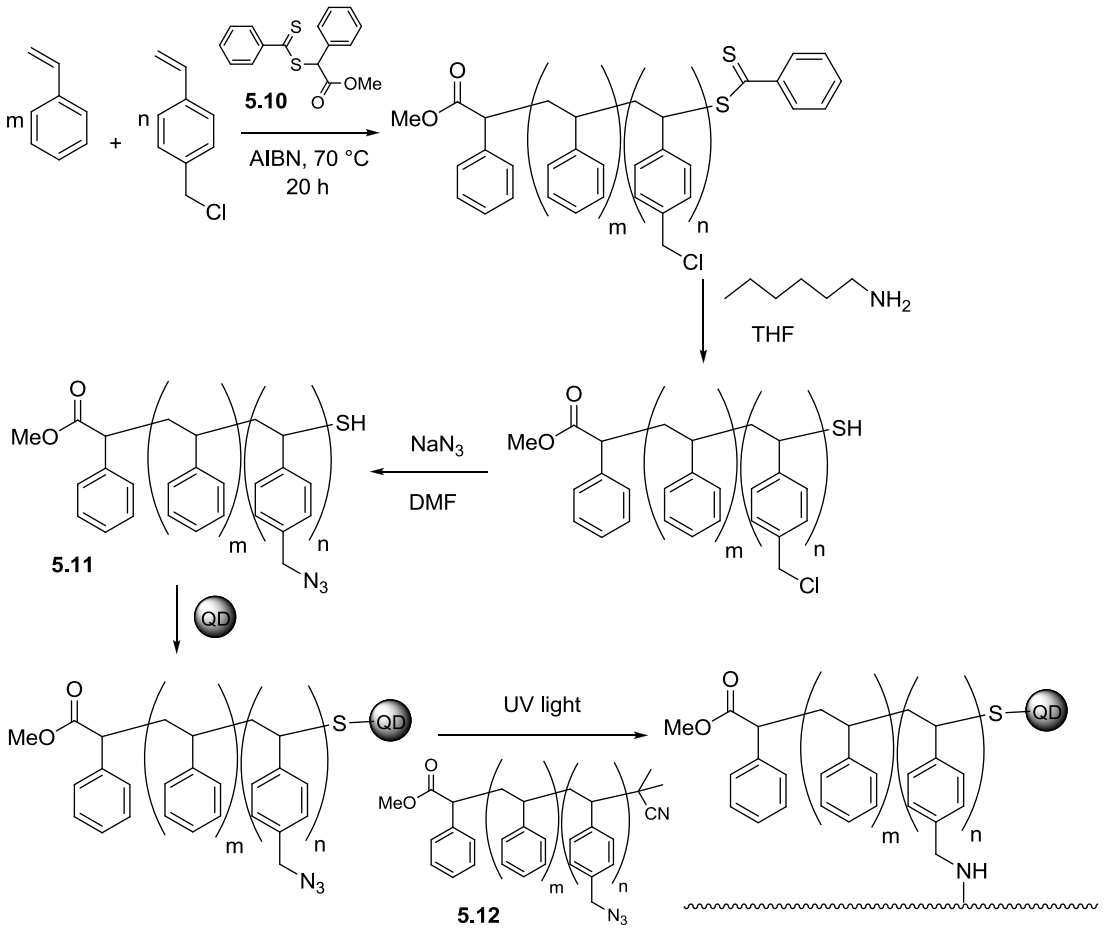


Scheme 5.5 Procedures for achieving self-assembly of multidentate ligands on quantum dots

These polar monovalent thioglycerol ligands were then replaced with copolymer ligands in dimethylsulfoxide (DMSO). It is energetically favorable for the linear multidentate polymer to wrap around the QD in a closed configuration, but this highly ordered structure is kinetically slow to form at room temperature. Stable, compactly coated QDs were produced only after heating for 1-2 h in DMSO.

Thiol terminated random copolymers for material applications have been prepared by RAFT polymerization (**Scheme 5.6**).[61] Styrene and *p*-chloromethylstyrene monomers were polymerized using AIBN as an initiator, and thioester **5.10** as the RAFT mediator. Aminolysis following by nucleophilic substitution with sodium azide provided thiol terminated photo cross-linkable copolymer **5.11** which was used to modify CdSe QD surfaces. UV cross-linking with copolymer **5.12** was carried out to fabricate an inorganic-organic self-assembled layer. UV irradiation of the azide groups hanging off the polymer backbone leads to the formation of highly reactive nitrene radicals, which undergo facile cross-linking with other polymer chains by C-H insertion, addition to double bonds, or H-abstraction.[62, 63] Based on this photo cross-linking reaction, the nanocomposite multilayers were prepared by a repetitive spin-coating and UV cross-linking sequence. The thickness of individual layers within multilayers could be controlled, ranging from a few nanometers to hundreds of nanometers, by varying the solution concentration and spin speed. These films may be utilized for the fabrication of

optical or electronic nanoscale devices such as display panels, nonvolatile memory, and organic thin film transistors.



Scheme 5.6 Bang and Cho's synthesis of photocross-linkable polymer containing QDs via living free radical polymerization (RAFT) followed by nucleophilic displacement with sodium azide and photo cross-linked layering

Beside nanoparticles, thiol terminated polymers are also used to functionalized CdSe[64] or CdS[65] nanorods to improve solubility and conductivity. Thiol-functionalized conducting polymers such as polythiophenes and

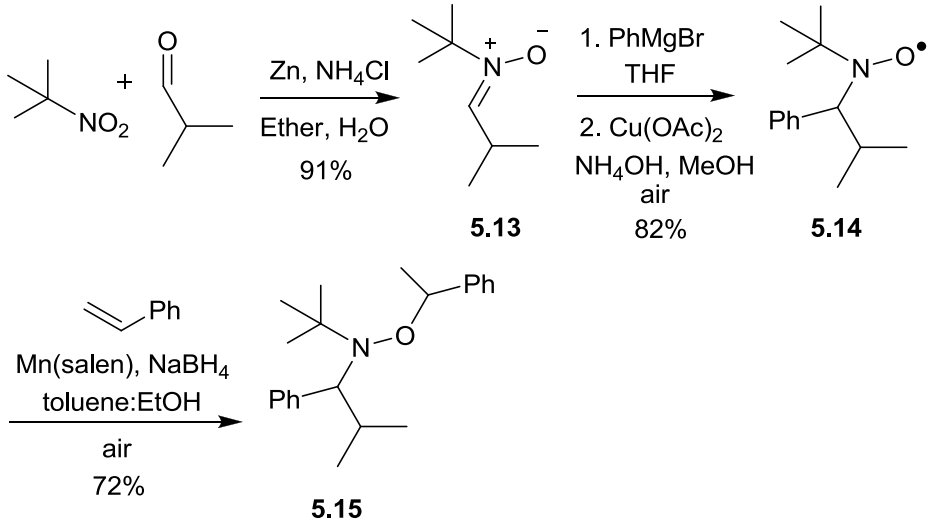
polyphenylacetylene directly attached to nanorod surfaces results in efficient charge transfer and easy processability, which may find technological applications in photoelectronic devices such as photovoltaic cells (PVCs), solar cells, and light-emitting diodes (LEDs).

The great affinity of thiols for the surface of CdSe QDs, coupled with powerful "living" polymerization methods for control over polymer size and weight sets the stage for the work to be described. The main goal of this project was to utilize "grafting from" method to introduce thiol terminated or disulfide initiator to the QD surface, rather than the more common "grafting to" approach. Since these initiators are much smaller than polymer, more surface area of the QDs will be occupied. Thiol terminated polymers growing from the resulting intiator-QD complex will provide greater protection from oxidation and aggregation of the QDs, resulting from a denser polymer population. In addition, nitroxide mediated radical polymerization (NMRP) affords unified polymer chain length, which is critical for improving optical and physical properties of the QDs.

5.4 Synthesis of TIPNO and Thiol-Derivatized Initiators

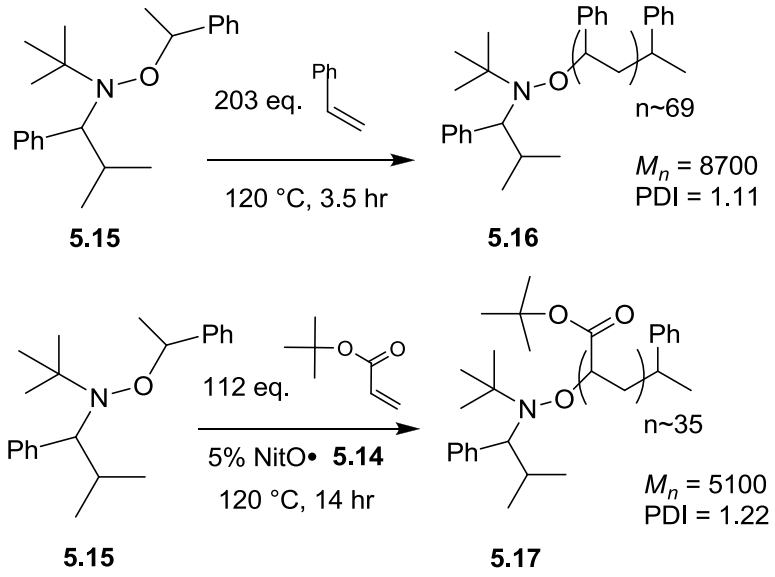
The first reactions that will be described involve the synthesis of the 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (TIPNO initiator)[12] as shown in **Scheme 5.7**. First, *N*-*tert*-butyl-α-isopropylnitrone was synthesized by the reaction of

2-methyl-2-nitropropane with isobutyraldehyde in the presence of ammonium chloride and zinc metal, using a mixture of water and diethyl ether as a solvent. Nitrone **5.13** was obtained in 91% yield. Reaction with two equivalents of phenylmagnesium bromide followed by addition of 5% copper acetate and air resulted in oxidation to give the nitroxide 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO) **5.14** in 82% yield after column chromatography. Following the modified procedure of Hawker *et al*.,[10] nitroxide **5.14** was combined with styrene along with a catalytic amount of achiral manganese salen catalyst[66] in a mixture of toluene and ethanol open to air. Afterwards, sodium borohydride was added to the reaction, and the reaction mixture was stirred open to the atmosphere overnight. Column chromatography afforded alkoxyamine **5.15** in 72% yield.



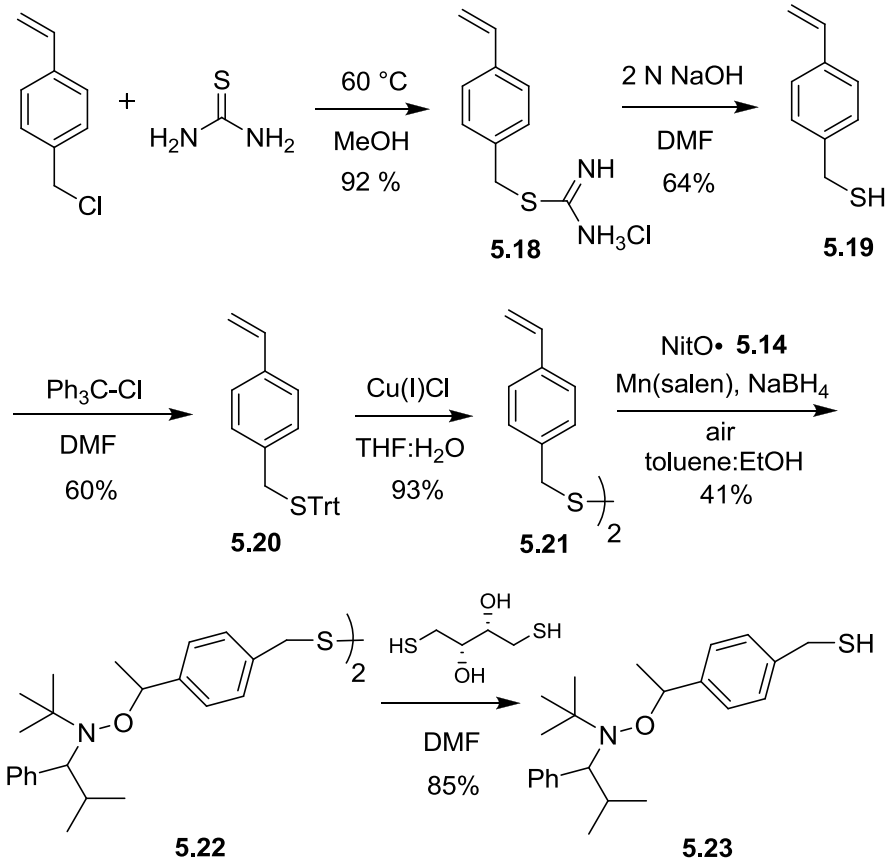
Scheme 5.7 Synthesis of TIPNO-based initiator **5.15**

Polystyrene **5.16** and poly-*tert*-butyl acrylate **5.17** were prepared using NMRP (**Scheme 5.8**). The TIPNO initiator was heated at 120 °C in a sealed ampule with 203 equivalents of styrene or 112 equivalents of *tert*- butyl acrylate monomer as a bulk polymerization. Since *tert*-butyl acrylate gets polymerized slower than styrene, free nitroxide **5.14** was added to keep the polymer chain "living" (*vide supra*). Oxygen was evacuated by three consecutive freeze/pump/thaw cycles. The polystyrene and poly-*tert*-butyl acrylate samples synthesized were a 69mer and a 35mer, respectively as determined by ^{1}H-NMR integration of the crude polymerization mixture.



Scheme 5.8 Polymerization of styrene and *tert*-butylacrylate using TIPNO initiator **5.15**

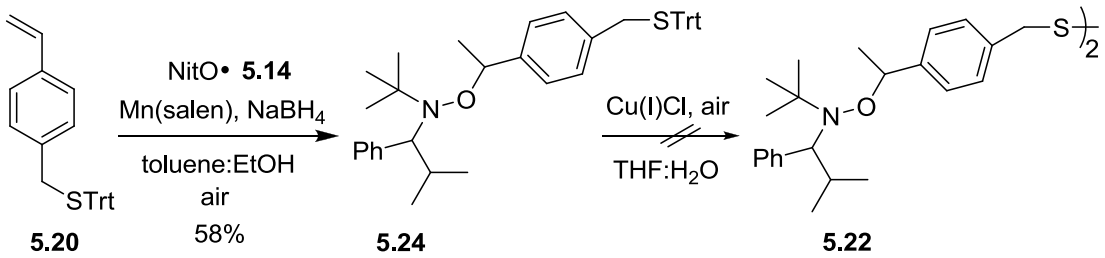
After the synthesis of the TIPNO initiator was complete, work began on the synthesis of disulfide and free thiol terminated initiators (**Scheme 5.9**). First, 2-(4-vinyl-benzyl) *iso*thiourea hydrochloride **5.18** was synthesized by S_N2 displacement of the commercially available 4-vinyl benzyl chloride with thiourea.[67] The *iso*thiouronium salt **5.18** was obtained following recrystallization in 92% yield, and was then hydrolyzed with 2 N sodium hydroxide[16] under nitrogen to give 4-vinyl phenyl methanethiol **5.19** in a 64% yield. The free thiol group was protected by S_N1



Scheme 5.9 Synthesis of free thiol initiator **5.23**

reaction with trityl chloride to afford (4-vinyl-benzyl)-trityl sulfide **5.20** in 60% yield after column chromatography. The trityl-protected thiol monomer was then simultaneously detritylated and oxidized by treatment with a catalytic amount of copper(I) chloride[68] open to atmosphere under ultrasonication in a mixture of tetrahydrofuran and water to form 1,2-bis (4-vinylbenzyl) disulfide **5.21** in 93% yield. The disulfide monomer **5.21** was used to make a disulfide initiator following the same conditions used for the standard synthesis of the TIPNO initiator. Alkoxyamine **5.22** was obtained in 41% yield after column chromatography, and then subjected to treatment with dithiothreitol (DTT) to give the free thiol initiator **5.23** in 85% yield.

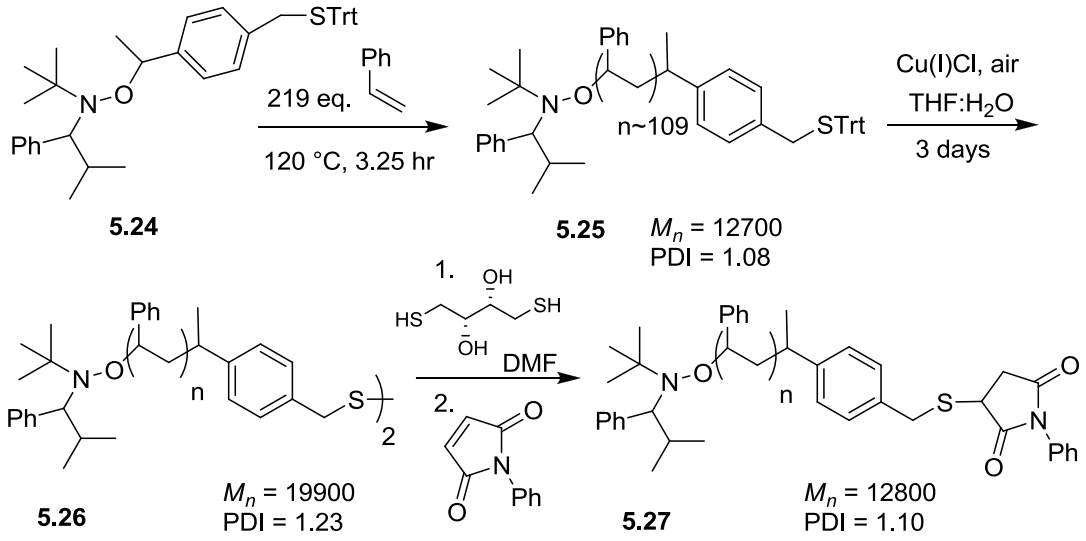
Since thiols are excellent hydrogen donors towards carbon radicals, during radical polymerization it is impossible to carry a free thiol, as termination of the radical chain would occur by hydrogen abstraction. The trityl-protected thiol monomer **5.20** was used to prepare the trityl-protected thiol initiator **5.24** using TIPNO nitroxide in 58% yield after column chromatography (**Scheme 5.10**). Attempts to make the disulfide initiator from this protected thiol initiator using copper(I) chloride and ultrasonication were unsuccessful. Oxidation with iodine was investigated,[69] and the desired disulfide initiator was formed. However, there were many impurities, including trityl hydroxide (originally from the trityl iodide) as a major impurity.



Scheme 5.10 Synthesis of trityl-protected thiol initiator **5.24**, and attempt to oxidize it with Cu(I)Cl and air to make central disulfide initiator **5.22**

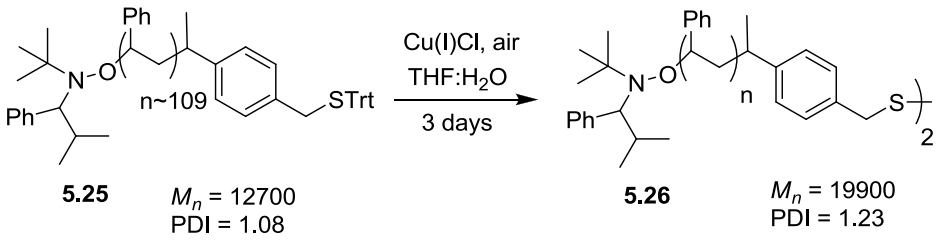
5.5 Polymerization with an Initiator bearing a Protected Thiol

The trityl-protected thiol initiator **5.24** was successfully used in NMRP, affording a '109mer' of polystyrene **5.25** (**Scheme 5.11**) as determined by ^{1}H-NMR



Scheme 5.11 Polymerization of styrene using trityl-protected initiator **5.24** followed by deprotection and oxidation to give polymer containing central disulfide **5.26**. Reduction of **5.26** with DTT and trapping with NPM provided NPM-protected thiol polymer **5.27**.

integration of the crude polymerization mixture. This initiator was easier to handle than the *tert*-butyldimethylsilyl (TBDMS)-protected thiol initiator made previously by graduate student Nicole Hill.[70] Polystyrene made from the TBDMS-protected initiator gave a high molecular weight shoulder in the GPC trace although the initiator had already been purified by flash column chromatography. It appears that a small amount of free thiol initiator was oxidized to the disulfide initiator, and polymers from this disulfide initiator were responsible for the high molecular weight shoulder. As a result, the TBDMS protected initiator was necessary to be rigorously purified via reverse-phase preparative HPLC, which gave only a small amount of pure TBDMS protected initiator after several purification runs were carried out. However, the trityl protected thiol initiator was easily purified, resulting in a clean GPC trace of the resulting polymer as shown for the peak on the right in **Figure 5.4**. As a post-polymerization modification, the assembly of two thiol terminated polymers into a disulfide polymer **5.26** was carried out by simultaneous detritylation and oxidation with catalytic amount of copper(I) chloride and air under ultrasonication for 3 days (**Scheme 5.11**). This transformation required only one step and was a clean reaction. On the other hand, hazardous hydrochloric acid and dioxane were used in the deprotection process of the TBDMS group, and the product had to be further oxidized in a subsequent step to make the disulfide polymer from the TBDMS-



5.25 M_n = 12700, PDI = 1.08

5.26 M_n = 19900, PDI = 1.23

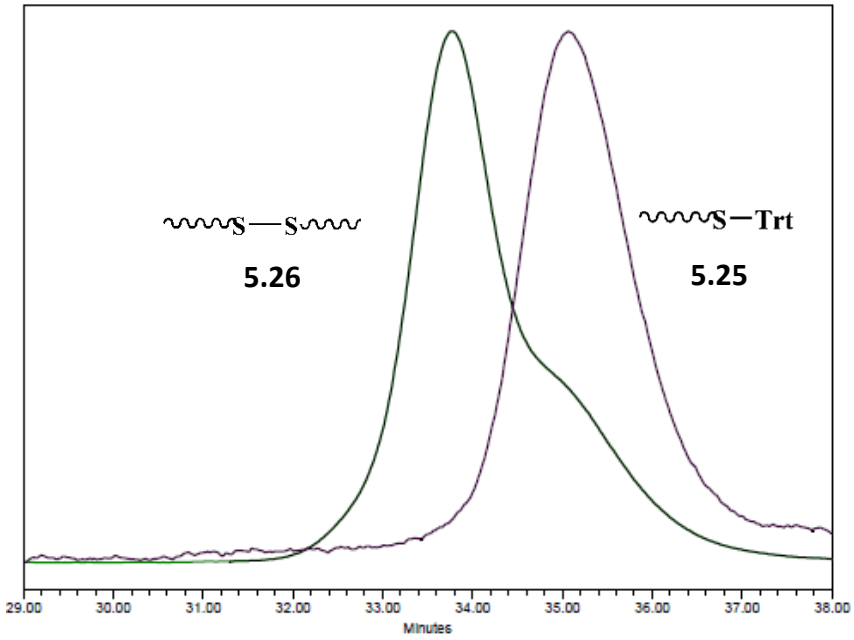


Figure 5.4 Overlay of GPC chromatographs of trityl-protected polystyrene **5.25** (right, M_n = 12 700, PDI = 1.08) and the resulting disulfide linked polystyrene **5.26** (left, M_n = 19 900, PDI = 1.23)

protected initiator.[70] A low molecular weight shoulder in the GPC trace of the disulfide polymer **5.26** (**Figure 5.4**) indicated that either thedeprotection or the oxidation did not reach completion, similar to the resulting disulfide polymer made from TBDMS-protected initiator (**Figure 5.5**), but the shoulder from polymer **5.26** prepared from the trityl-protected initiator was much smaller. The majority of the

chains were deprotected and oxidized to the disulfide, resulting in an increase in molecular weight from 12700 to 19900. The raw data obtained from the GPC trace of the disulfide polymer **5.26** was analyzed using multi-peak curve fitting to separate the overlapping peaks of the resulting disulfide polymer and the unreacted trityl-protected polymer **5.25** (**Figure 5.6**). The curve fit summation peak (bright green) is very close to the original GPC trace of the disulfide polymer **5.26** (dark green), corroborating the accuracy of the curve fitting protocol. From the curve fit, the number (M_n) and weight average (M_w) molecular weights, polydispersity index (PDI), and percent composition (% Comp) of each component in the mixture was

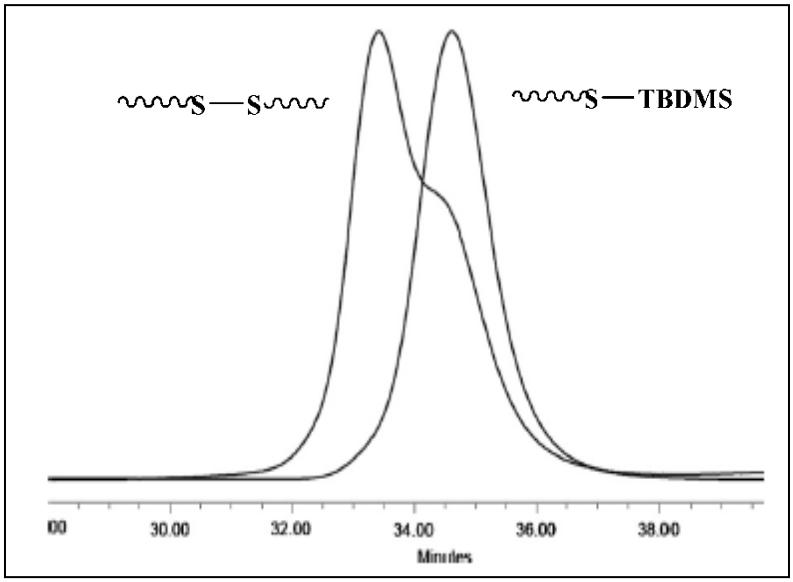


Figure 5.5 Overlay of GPC chromatographs of Nicole Hill's TBDMS-protected polystyrene (right, M_n = 15 800, PDI = 1.13) and the resulting disulfide linked polystyrene (left, M_n = 23 000, PDI = 1.22)

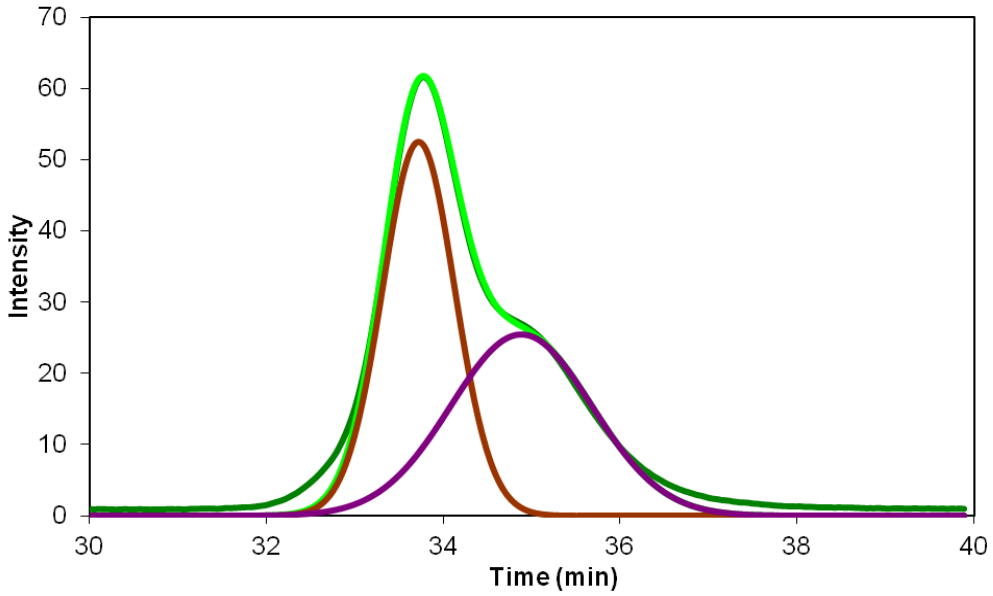


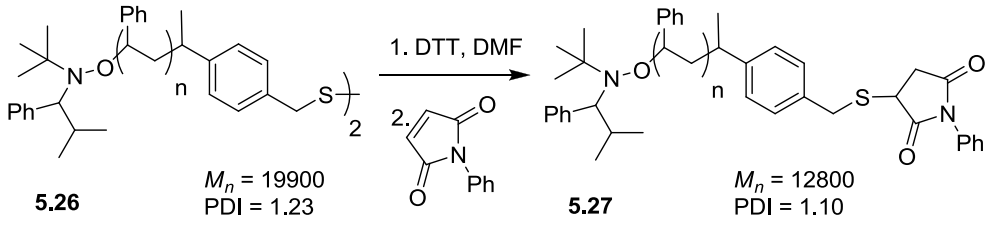
Figure 5.6 GPC chromatograph of disulfide linked polystyrene **5.26** (dark green), with computationally derived Gaussian curves: curve fit summation (bright green), disulfide linked polystyrene (brown), unreacted trityl-protected polystyrene (purple)

determined (**Table 5.1**). The data analysis indicated that 52% of the sample contained disulfide, and 48% of trityl-protected polymer remained unreacted. The disulfide polymer sample **5.26** was subjected to treatment with dithiothreitol to cleave the disulfide bond followed by capping the free thiol groups via Michael addition to *N*-phenylmaleimide (NPM)[71] to prevent re-oxidation to the disulfide (**Scheme 5.11**). The reduction gave polymer **5.27** of half the original molecular weight, indicating the reversibility of disulfide formation as shown in **Figure 5.7**.

Table 5.1 Composition and molecular weight data calculated from multi-peak curve fitting analysis of raw data obtained from GPC analysis of disulfide polystyrene **5.26**

Polymer	M_n	M_w	PDI	% Comp
mixture 5.26	19 909[a]	24474[a]	1.23[a]	-
disulfide	28 466[b]	29 995[b]	1.05[b]	52[b]
trityl	16 884[b]	19 855[b]	1.18[b]	48[b]

[a]Values obtained from GPC analysis
[b]Values obtained from multi-peak curve fitting



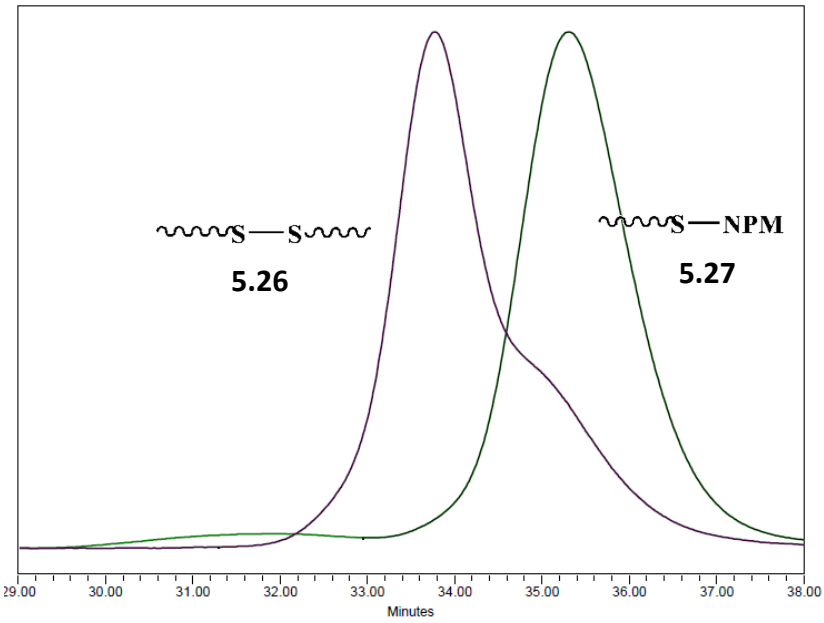
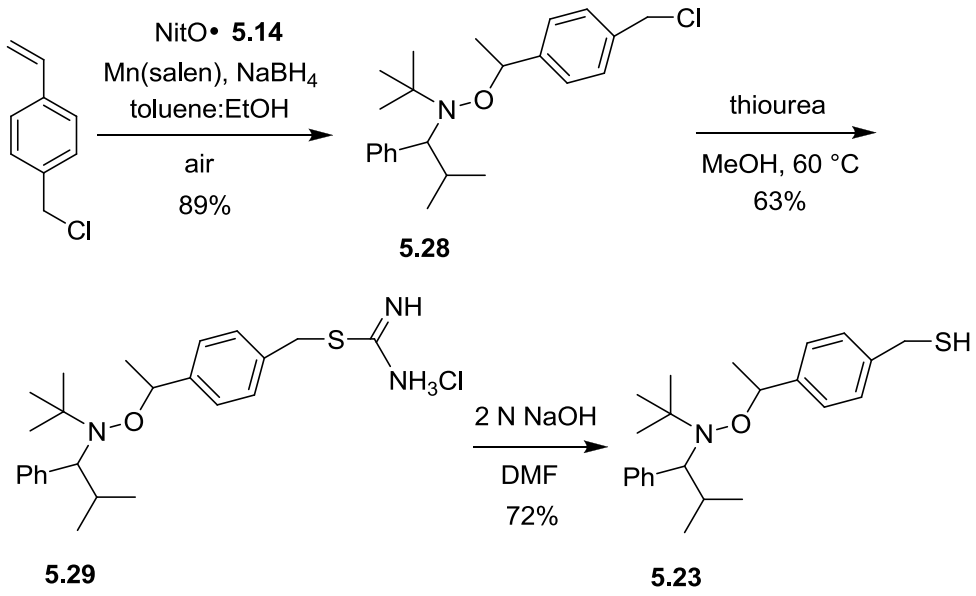


Figure 5.7 Overlay of GPC chromatographs for disulfide linked polystyrene **5.26** (left, M_n = 19 900, PDI = 1.23) and maleimide-trapped thiol terminated polystyrene **5.27** following disulfide cleavage (right, M_n = 12 800, PDI = 1.10)

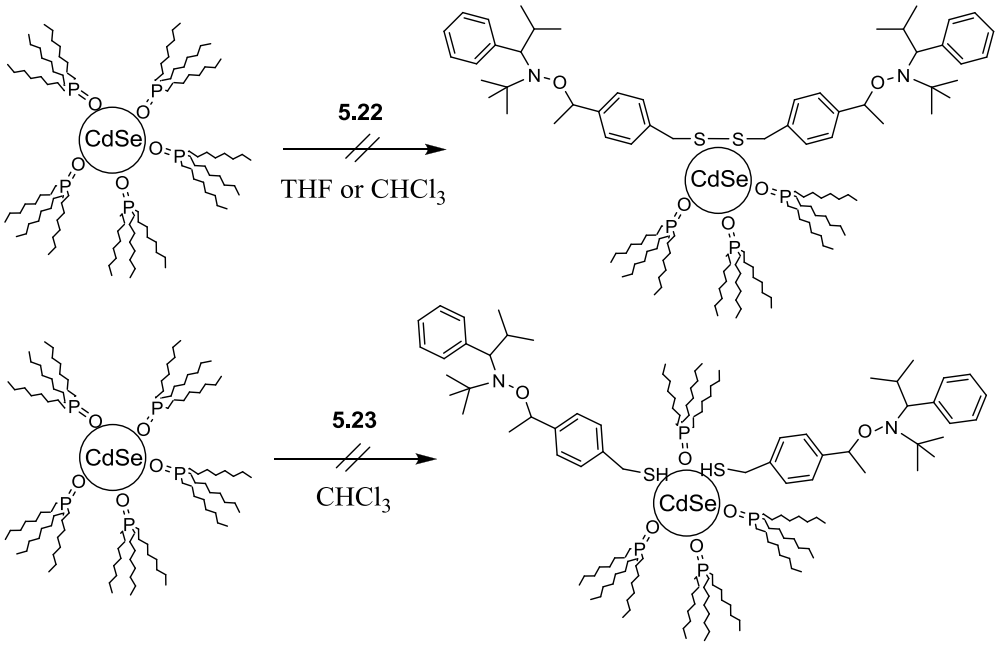
Excess sodium borohydride was used in the preparation of alkoxyamine **5.22** from disulfide **5.21**, perhaps resulting in partial reduction of the disulfide bond. In order to avoid using sodium borohydride in the presence of a disulfide bond, and to reduce synthetic steps, 4-vinylbenzyl chloride was combined with TIPNO nitroxide to make the previously reported benzyl chloride initiator[10] **5.28** in 89% yield after column chromatography (**Scheme 5.12**). The benzyl chloride *N*-alkoxyamine **5.28** was heated overnight in methanol with thiourea to give the thiouronium salt initiator **5.29**, isolated as the hydrochloride salt and purified via flash column chromatography in 63% yield. This thiourea derivative was deprotected with 2 N sodium hydroxide in dimethylformamide under nitrogen to afford 72% yield of the known free thiol initiator[70] **5.23**.



Scheme 5.12 Alternative route to make free thiol initiator **5.23**

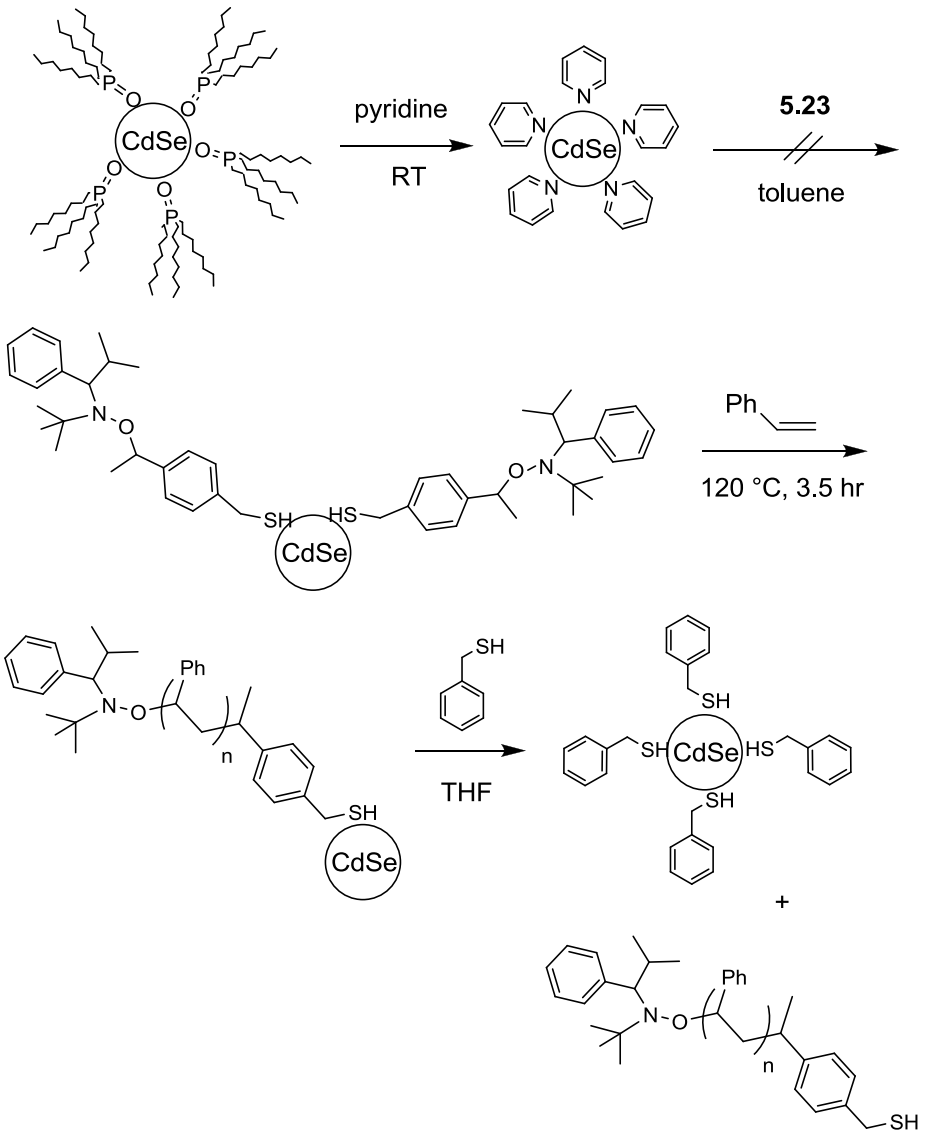
5.6 Attempts at CdSe Quantum Dot Encapsulation

Disulfide and free thiol initiators were used to functionalize the surface of CdSe quantum dots (**Scheme 5.13**). Following a 'grafting from' method, which gives denser polymer chains coverage on nanoparticle surface than the 'grafting to' method, it was planned to put the initiators on the surface and then carry out polymerization by NMRP. An initial attempt by direct ligand exchange of a TOPO group on the CdSe surface by the disulfide initiator **5.22** in tetrahydrofuran (THF) at room temperature was unsuccessful. There were no ^{1}H NMR peaks characteristic of the disulfide initiator from CdSe sample, but large peaks were seen from THF.



Scheme 5.13 Attempts to put either central disulfide initiator **5.22** or free thiol initiator **5.23** on a CdSe QD surface were unsuccessful.

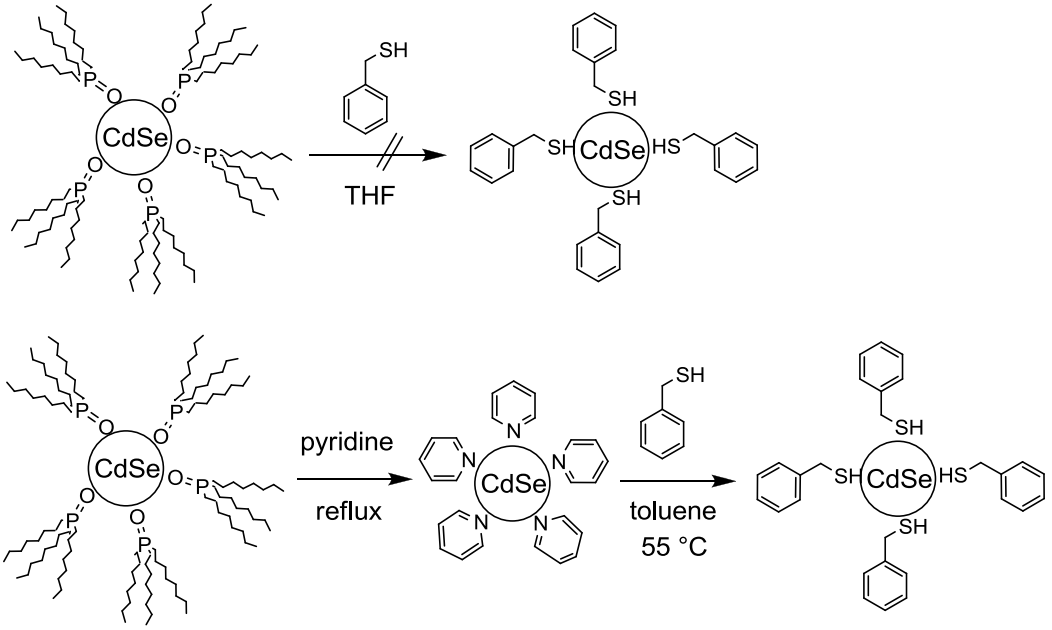
Chloroform was used as solvent to avoid the appearance of multiple solvent peaks, and much more disulfide initiator with respect to the TOPO-capped CdSe was added. Again, there were no ^{1}H NMR peaks corresponding to the initiator, but big peaks were observed from the TOPO groups. The second attempt was carried out using the free thiol initiator **5.23** under nitrogen, but it was still unsuccessful. The next attempt (**Scheme 5.14**) utilized pyridine ligand exchange at room temperature; the high affinity of the thiol group for the Cd surface atoms with respect to the amine was expected to drive the exchange of the pyridine for the thiol initiator.[72] A characteristic methine proton peak from the alkoxyamine initiator at 4.9 ppm was observed, but there were no methyl proton peaks corresponding to the initiator. The polymerization with styrene monomer was attempted on this functionalized CdSe. Polystyrene assumed to be on the CdSe surface was removed by addition of benzyl thiol. Molecular weight analysis of the resultant polymer gave M_n = 166600 amu and PDI = 1.89, indicating that autopolymerization of styrene in the bulk solution occurred rather than NMRP from the QD surface. It was concluded the NMR peak at 4.9 ppm was not from the thiol initiator.



Scheme 5.14 Attempt to exchange TOPO with pyridine at room temperature, followed by the exchange with free thiol initiator **5.23**, and then polymerization with styrene was unsuccessful.

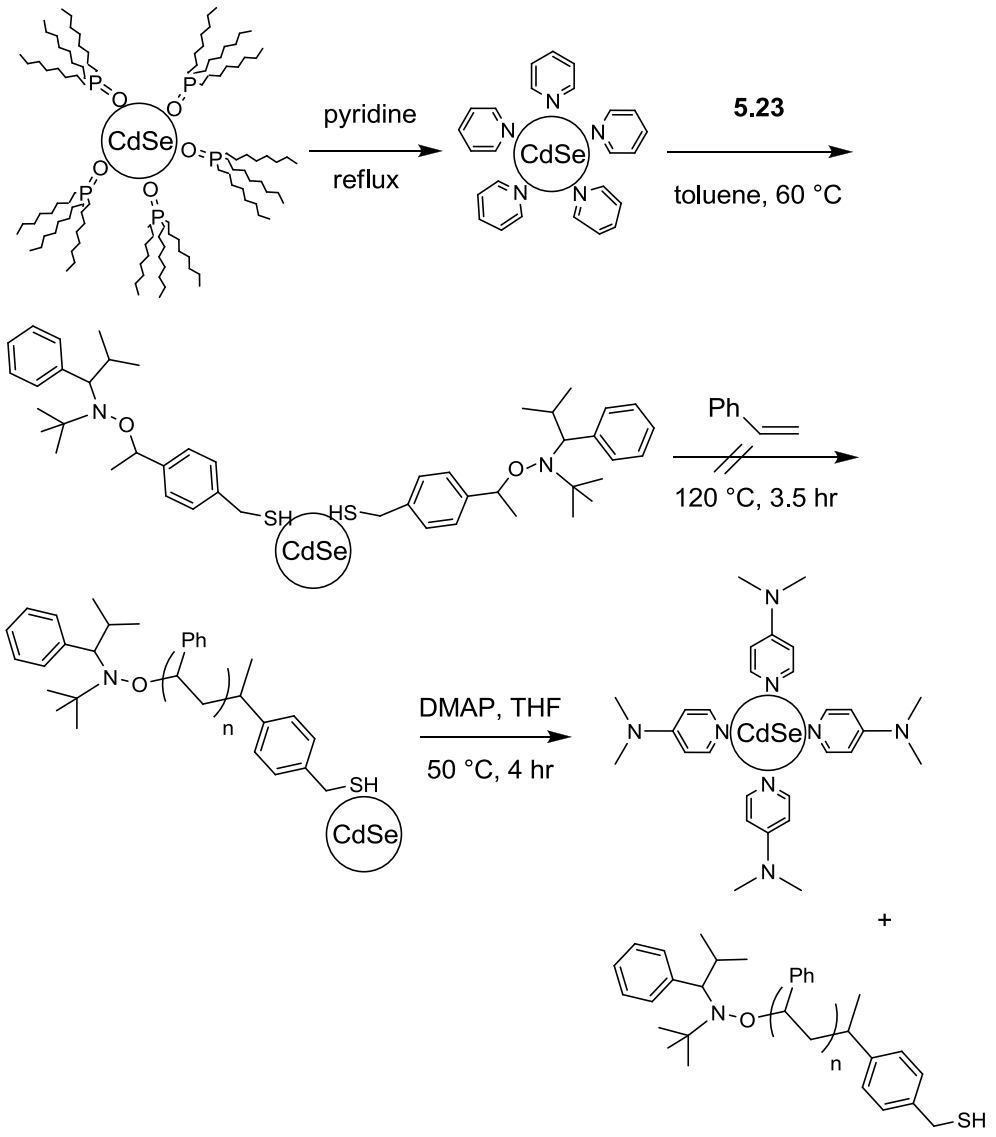
The quantum dot encapsulation was re-attempted with a model thiol compound, benzyl thiol (**Scheme 5.15**). Without pyridine exchange, no thiol was

introduced to the quantum dot surface. On the other hand, pyridine exchange under reflux, and subsequent thiol exchange in toluene[73] at 55 °C gave CdSe QDs which showed proton peaks of benzyl thiol. This same protocol was then used



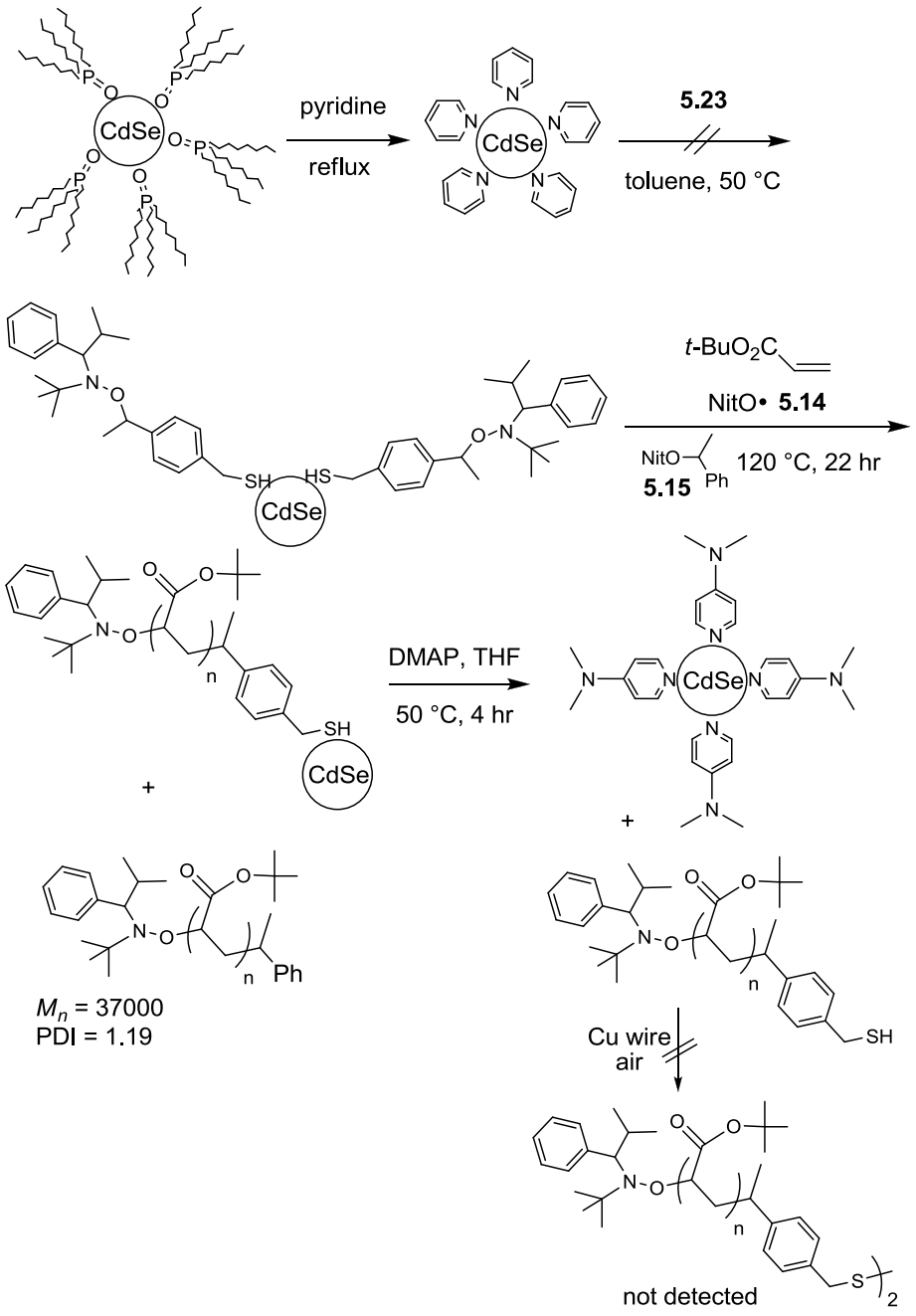
Scheme 5.15 Attempt to exchange TOPO directly with benzyl thiol was unsuccessful. However, refluxing TOPO with pyridine followed by the exchange with benzyl thiol gave the desired thiol-capped quantum dots.

with the free thiol initiator **5.23** (**Scheme 5.16**), and ^{1}H NMR showed characteristic peaks of the alkoxyamine initiator. This thiol-functionalized CdSe was subjected to polymerization with styrene monomer, and polystyrene was removed from the surface by exchange with 4-methylaminopyridine (DMAP).[72] The GPC trace showed an M_n = 156900 amu and PDI = 1.71, again indicating that autopolymerization of bulk styrene had occurred.



Scheme 5.16 Attempt to exchange TOPO with pyridine at reflux followed by exchange with free thiol initiator **5.23**, and then polymerization with styrene was unsuccessful.

Polymerization with *tert*-butyl acrylate monomer in the presence of free nitroxide **5.14**, rather than styrene monomer was investigated to avoid the autopolymerization. TIPNO Alkoxyamine initiator **5.15** was also added to the reaction ampule to compare the resulting polymer properties with those grown on the nanoparticle surface (**Scheme 5.17**). The reaction mixture was centrifuged to separate polymer-QD complex from the free polymer growing from the TIPNO initiator **5.15**. Polymer on the QD surface was then exchanged with DMAP. Both the polymer from CdSe QDs and the free polymer from the TIPNO initiator **5.15** showed approximately the same properties: M_n = 34000 amu and M_n = 37000 amu, respectively; with both showing a PDI = 1.19. However, after oxidation with copper wire and bubbling with air, what was supposed to be the thiol-terminated poly-*tert*-butyl acrylate gave the same molecular weight instead of the double mass. This indicates that the isolated polymer from the QD surface does not have thiol functionality at the end of the chain. The intiator-quantum dot complex might be unstable under the high temperature (120 °C) of the polymerization conditions.



Scheme 5.17 Attempt to exchange TOPO with pyridine at reflux followed by the exchange with free thiol initiator **5.23**, and then polymerization with *tert*-butylacrylate was unsuccessful.

5.7 Conclusion

Thiol-derivatized *N*-alkoxyamines including free thiol, disulfide, and trityl-protected thiol initiators were synthesized. Trityl-protected thiol chain-end functionalized polystyrene of well-defined molecular weight and polydispersity was prepared using NMRP. Deprotection of the trityl group and oxidation under mild conditions provided disulfide linked polystyrene of approximately double the molecular weight. Since the redox properties of thiol/disulfide formation is reversible, reduction of the disulfide linked polystyrene, followed by trapping with *N*-phenylmaleimide (NPM) resulted in a NPM-protected thiol terminated polystyrene with the same molecular weight as prior to oxidation.

Attempts were made to attach free thiol and disulfide initiators on the surface of CdSe nanoparticles. It was hoped to grow polymers from these surface-bound initiators by NMRP, to capsulate and stabilize the quantum dots. Direct exchange of the sulfur-derivatized initiator with TOPO ligand on the CdSe surface, followed by polymerization gave polystyrene of high molecular weight and PDI > 1.5, indicating autopolymerization of styrene rather than NMRP. Ligand exchange with pyridine followed by exchange with free thiol initiator was also unsuccessful. The final conclusion is either that the initiators were never successfully attached to the quantum dot surface, or the initiator-quantum dot complex was labile to the 120 °C temperature required for NMRP polymerization. The “grafting-to” approach might

be an alternative method to introduce pre-formed thiol terminated polymers, or polymers containing a disulfide such as **5.26** to CdSe QD surfaces.

5.8 References

1. Malenovska, M.; Martinez, S.; Neouze, M. A.; Schubert, U., *European Journal of Inorganic Chemistry* **2007,** (18), 2609-2611.

2. Grubbs, R. B., *Polymer Reviews* **2007,** *47* (2), 197-215.

3. Vollhardt, K. P. C.; Schore, N. E., *Organic Chemistry, Structure and Function* W. H. Freeman and Company: New York, 2003.

4. Szwarc, M., *Nature* **1956,** *178* (4543), 1168-1169.

5. Hawker, C. J.; Bosman, A. W.; Harth, E., *Chemical Reviews* **2001,** *101* (12), 3661-3688.

6. Jenkins, A. D.; Jones, R. G.; Moad, G., *Pure and Applied Chemistry* **2010,** *82* (2), 483-491.

7. Rizzardo, E.; Solomon, D. H., *Polymer Bulletin* **1979,** *1* (8), 529-534.

8. Moad, G.; Rizzardo, E.; Solomon, D. H., *Macromolecules* **1982,** *15* (3), 909-914.

9. Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K., *Macromolecules* **1993,** *26* (11), 2987-2988.

10. Dao, J.; Benoit, D.; Hawker, C. J., *Journal of Polymer Science Part A-Polymer Chemistry* **1998,** *36* (12), 2161-2167.

11. Bisht, H. S.; Chatterjee, A. K., *Journal of Macromolecular Science-Polymer Reviews* **2001,** *C41* (3), 139-173.

12. Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J., *Journal of the American Chemical Society* **1999,** *121* (16), 3904-3920.

13. Grimaldi, S.; Finet, J. P.; Le Moigne, F.; Zeghdaoui, A.; Tordo, P.; Benoit, D.; Fontanille, M.; Gnanou, Y., *Macromolecules* **2000,** *33* (4), 1141-1147.

14. Nilsen, A.; Braslau, R., *Journal of Polymer Science Part A-Polymer Chemistry* **2006,** *44* (2), 697-717.

15. Rahmat, D.; Sakloetsakun, D.; Shahnaz, G.; Perera, G.; Kaindl, R.; Bernkop-Schnurch, A., *International Journal of Pharmaceutics* **2011,** *411* (1-2), 10-17.

16. Yamaguchi, K.; Kato, T.; Hirao, A.; Nakahama, S., *Makromolekulare Chemie-Rapid Communications* **1987,** *8* (4), 203-207.

17. York, A. W.; Huang, F. Q.; McCormick, C. L., *Biomacromolecules* **2010,** *11* (2), 505-514.

18. Lee, C. U.; Roy, D.; Sumerlin, B. S.; Dadmun, M. D., *Polymer* **2010,** *51* (6), 1244-1251.

19. Garamszegi, L.; Donzel, C.; Carrot, G.; Nguyen, T. Q.; Hilborn, J., *Reactive & Functional Polymers* **2003,** *55* (2), 179-183.

20. Zhu, N.; Ling, J.; Zhu, Y. H.; Sun, W. L.; Shen, Z. Q., *Journal of Polymer Science Part A-Polymer Chemistry* **2010,** *48* (19), 4366-4369.

21. Warren, N. J.; Muise, C.; Stephens, A.; Armes, S. P.; Lewis, A. L., *Langmuir* **2012,** *28* (5), 2928-2936.

22. Hilf, S.; Kilbinger, A. F. M., *Macromolecules* **2009,** *42* (12), 4127-4133.

23. Kim, B. J.; Bang, J.; Hawker, C. J.; Chiu, J. J.; Pine, D. J.; Jang, S. G.; Yang, S. M.; Kramer, E. J., *Langmuir* **2007,** *23* (25), 12693-12703.

24. Tanaka, M.; Fujita, R.; Nishide, H., *Polymer* **2007,** *48* (20), 5884-5888.

25. Salmaso, S.; Caliceti, P.; Amendola, V.; Meneghetti, M.; Magnusson, J. P.; Pasparakis, G.; Alexander, C., *Journal of Materials Chemistry* **2009,** *19* (11), 1608-1615.

26. Bae, S. K.; Lee, S. Y.; Hong, S. C., *Reactive & Functional Polymers* **2011,** *71* (2), 187-194.

27. Anraku, Y.; Takahashi, Y.; Kitano, H.; Hakari, M., *Colloids and Surfaces B-Biointerfaces* **2007,** *57* (1), 61-68.

28. Chung, Y. C.; Chen, I. H.; Chen, C. J., *Biomaterials* **2008,** *29* (12), 1807-1816.

29. Aldana, J.; Lavelle, N.; Wang, Y. J.; Peng, X. G., *Journal of the American Chemical Society* **2005,** *127* (8), 2496-2504.

30. Gaponik, N., *Journal of Materials Chemistry* **2010,** *20* (25), 5174-5181.

31. Eychmuller, A.; Rogach, A. L., *Pure and Applied Chemistry* **2000,** *72* (1-2), 179-188.

32. Majumder, M.; Karan, S.; Mallik, B., *Journal of Luminescence* **2011,** *131* (12), 2792-2802.

33. Jun, S.; Jang, E. J.; Chung, Y. S., *Nanotechnology* **2006,** *17* (19), 4806-4810.

34. Sobhana, S. S. L.; Devi, M. V.; Sastry, T. P.; Mandal, A. B., *Journal of Nanoparticle Research* **2011,** *13* (4), 1747-1757.

35. Gerion, D.; Pinaud, F.; Williams, S. C.; Parak, W. J.; Zanchet, D.; Weiss, S.; Alivisatos, A. P., *Journal of Physical Chemistry B* **2001,** *105* (37), 8861-8871.

36. Liu, I. S.; Lo, H. H.; Chien, C. T.; Lin, Y. Y.; Chen, C. W.; Chen, Y. F.; Su, W. F.; Liou, S. C., *Journal of Materials Chemistry* **2008,** *18* (6), 675-682.

37. Behrendt, J. M.; Afzaal, M.; Alexander, L. M.; Bradley, M.; Hine, A. V.; Nagel, D.; O'Brien, P.; Presland, K.; Sutherland, A. J., *Journal of Materials Chemistry* **2009,** *19* (2), 215-221.

38. Mu, J.; Gao, X. B.; Zhang, Y. Y.; Sun, H.; Liu, L. Y., *Journal of Dispersion Science and Technology* **2006,** *27* (1), 77-81.

39. Sathyamoorthy, R.; Sudhagar, P.; Kumar, R. S.; Sathyadevan, T. M., *Crystal Research and Technology* **2010,** *45* (1), 99-103.

40. El-Sadek, M. S. A.; Kumar, J. R.; Babu, S. M., *Current Applied Physics* **2010,** *10* (1), 317-322.

41. Rogach, A. L.; Franzl, T.; Klar, T. A.; Feldmann, J.; Gaponik, N.; Lesnyak, V.; Shavel, A.; Eychmuller, A.; Rakovich, Y. P.; Donegan, J. F., *Journal of Physical Chemistry C* **2007,** *111* (40), 14628-14637.

42. Poznyak, S. K.; Osipovich, N. P.; Shavel, A.; Talapin, D. V.; Gao, M. Y.; Eychmuller, A.; Gaponik, N., *Journal of Physical Chemistry B* **2005,** *109* (3), 1094-1100.

43. Gaponik, N.; Rogach, A. L., *Physical Chemistry Chemical Physics* **2010,** *12* (31), 8685-8693.

44. Premachandran, R.; Banerjee, S.; John, V. T.; McPherson, G. L.; Akkara, J. A.; Kaplan, D. L., *Chemistry of Materials* **1997,** *9* (6), 1342-1347.

45. Sudeep, P. K.; Emrick, T., *Polymer Reviews* **2007,** *47* (2), 155-163.

46. Skaff, H.; Emrick, T., *Angewandte Chemie-International Edition* **2004,** *43* (40), 5383-5386.

47. Sill, K.; Emrick, T., *Chemistry of Materials* **2004,** *16* (7), 1240-1243.

48. Skaff, H.; Ilker, M. F.; Coughlin, E. B.; Emrick, T., *Journal of the American Chemical Society* **2002,** *124* (20), 5729-5733.

49. Hou, X. D.; Li, Q. B.; Jia, L.; Li, Y.; Zhu, Y. D.; Cao, A. M., *Macromolecular Bioscience* **2009,** *9* (6), 551-562.

50. Mitchell, G. P.; Mirkin, C. A.; Letsinger, R. L., *Journal of the American Chemical Society* **1999,** *121* (35), 8122-8123.

51. Diltemiz, S. E.; Say, R.; Buyuktiryaki, S.; Hur, D.; Denizli, A.; Ersoz, A., *Talanta* **2008,** *75* (4), 890-896.

52. Yildiz, I.; McCaughan, B.; Cruickshank, S. F.; Callan, J. F.; Raymo, F. M., *Langmuir* **2009,** *25* (12), 7090-7096.

53. You, C. J.; Wilmes, S.; Beutel, O.; Lochte, S.; Podoplelowa, Y.; Roder, F.; Richter, C.; Seine, T.; Schaible, D.; Uze, G.; Clarke, S.; Pinaud, F.; Dahan, M.; Piehler, J., *Angewandte Chemie-International Edition* **2010,** *49* (24), 4108-4112.

54. Yildiz, I.; Deniz, E.; McCaughan, B.; Cruickshank, S. F.; Callan, J. F.; Raymo, F. M., *Langmuir* **2010,** *26* (13), 11503-11511.

55. Jana, N. R.; Erathodiyil, N.; Jiang, J.; Ying, J. Y., *Langmuir* **2010,** *26* (9), 6503-6507.

56. Cui, Y.; Gong, X. Q.; Zhu, S. J.; Li, Y. H.; Su, W. Y.; Yang, Q. H.; Chang, J., *Journal of Materials Chemistry* **2012,** *22* (2), 462-469.

57. Huang, B. H.; Tomalia, D. A., *Journal of Luminescence* **2005,** *111* (4), 215-223.

58. Wisher, A. C.; Bronstein, I.; Chechik, V., *Chemical Communications* **2006,** (15), 1637-1639.

59. Liu, L.; Guo, X. H.; Li, Y.; Zhong, X. H., *Inorganic Chemistry* **2010,** *49* (8), 3768-3775.

60. Smith, A. M.; Nie, S., *Journal of the American Chemical Society* **2008,** *130* (34), 11278-11279.

61. Lee, S.; Lee, B.; Kim, B. J.; Park, J.; Yoo, M.; Bae, W. K.; Char, K.; Hawker, C. J.; Bang, J.; Cho, J. H., *Journal of the American Chemical Society* **2009,** *131* (7), 2579-2587.

62. Roy, D.; Basu, P. K.; Raghunathan, P.; Eswaran, S. V., *Magnetic Resonance in Chemistry* **2003,** *41* (9), 671-678.

63. Yasuda, N.; Yamamoto, S.; Wada, Y.; Yanagida, S., *Journal of Polymer Science Part A-Polymer Chemistry* **2001,** *39* (24), 4196-4205.

64. Sih, B. C.; Wolf, M., *Journal of Physical Chemistry C* **2007,** *111* (46), 17184-17192.

65. Xu, H. P.; Xie, B. Y.; Yuan, W. Z.; Sun, J. Z.; Yang, F.; Dong, Y. Q.; Qin, A. J.; Zhang, S.; Wang, M.; Tang, B. Z., *Chemical Communications* **2007,** (13), 1322-1324.

66. Choudary, B. M.; Kantam, M. L.; Bharathi, B.; Reddy, C. R. V., *Journal of Molecular Catalysis A-Chemical* **2001,** *168* (1-2), 69-73.

67. Watanabe, S.; Nakahama, S.; Yamaguchi, K., *Makromolekulare Chemie-Macromolecular Chemistry and Physics* **1991,** *192* (8), 1891-1902.

68. Ma, M.; Zhang, X.; Peng, L. L.; Wang, J. B., *Tetrahedron Letters* **2007,** *48* (7), 1095-1097.

69. Kamber, B.; Hartmann, A.; Eisler, K.; Riniker, B.; Rink, H.; Sieber, P.; Rittel, W., *Helvetica Chimica Acta* **1980,** *63* (4), 899-915.

70. Hill, N. L.; Jarvis, J. L.; Pettersson, F.; Braslau, R., *Reactive & Functional Polymers* **2008,** *68* (1), 361-368.

71. Chujo, Y.; Sada, K.; Naka, A.; Nomura, R.; Saegusa, T., *Macromolecules* **1993,** *26* (5), 883-887.

72. Wuister, S. F.; Donega, C. D.; Meijerink, A., *Journal of Physical Chemistry B* **2004,** *108* (45), 17393-17397.

73. Zhang, Q. L.; Russell, T. P.; Emrick, T., *Chemistry of Materials* **2007,** *19* (15), 3712-3716.

Chapter 6: Experimental Section

6.1 General Considerations

6.1.1 General Materials

Triethylamine (Fisher) and pyridine (Aldrich, 99.9%) were distilled over calcium hydride. Methyl acrylate (Sigma-Aldrich, 99%), styrene (Fisher, 99.9%) and *tert*-butyl acrylate (Sigma-Aldrich, 98%) were distilled under vacuum immediately before use. Diethyl ether (Fisher, 99.1%) was distilled from sodium/benzophenone. Acetronitrile, dichloromethane, tetrahydrofuran, methanol and toluene were obtained from a PureSolv solvent purification system (SPS) manufactured by Innovative Technologies, Inc. when anhydrous conditions were required. All other solvents were used as received. Water was deionized. Manganese salen catalyst was prepared following the procedure of Choudary *et al*.[1] Dess-Martin periodinane was prepared following the procedure of Mullins *et al*.[2] Molecular sieves (4 Å, 1.6 mm pellets, Aldrich) were activated by heating in an oven at 200 °C overnight. All other reagents were used as received.

The following reagents were purchased from Acros Organics: 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO, 98%), methanesulfonyl chloride (99.5%), methyl vinyl ketone (95%), sodium hydride (60% dispersion in mineral oil), tetrabutylammonium fluoride (TBAF, 1.0 M in THF containing 5% water), 1,4-

cyclohexadiene (97%), lead dioxide (97%), thiourea (reagent grade, ACS), 4-vinylbenzyl chloride (90%), 3,4-dihydro-*2H*-pyran (99%), vinyl bromide (1.0 M in THF), methylmagnesium bromide (1.0 M in THF), iodomethane (99%), (1-bromoethyl)benzene (97%), lead (IV) oxide (97%), sodium nitrite, 2-methyl-2-butene (99%), and *N*,*N*-diisopropylethylenediamine (98%). The following reagents were purchased from Fisher Scientific: zinc powder (99%), ammonium chloride (99.7%), succinic anhydride (99%), ethylenediamine (99%), triethylborane (1.0 M in THF), sodium borohydride (98%), sodium hydroxide (98.7%), copper(I) chloride (99%), carbon disulfide (100.0%), magnesium turnings and concentrated hydrochloric acid (12 M). The following reagents were purchased from Sigma-Aldrich: trityl chloride (98%), triphenylphosphine (99%), 4-dimethylaminopyridine (DMAP, 99%), *n*-butyllithium (1.6 M in hexanes), concentrated ammonium hydroxide (7.4 N), glacial acetic acid (17.4 N), 4-phenylbutyric acid (99%), benzylamine (99%), DL-dithiothreitol (99%), *N*-phenylmaleimide (97%), nitrobenzene (98%), *p*-toluenesulfonic acid monohydrate (99%), 1,3-dicyclohexylcarbodiimide (DCC, 99%), sodium chlorite, sodium phosphate (99%), and manganese dioxide (99%). The following reagents were purchased from Alfa Aesar: phenylhydrazine (97%), phenylmagnesium bromide (3.0 M in diethyl ether), isobutyraldehyde (98%), and diisobutylaluminum hydride (DIBAL-H, 1.0 M in hexane), δ-valerolactone (98%), L-ascorbic acid, sodium salt (99%), zinc bromide (98%), acrolein (97%), 1-pyrenecarboxaldehyde (99%) and

hexamethylphosphorus triamide (97%). The following reagents were purchased from TCI America: 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPOL, 98%), 2-methyl-2-nitropropane (98%) and *N*,*O*-dimethylhydroxylamine (98%), and propargyl bromide (97%). Diethylphosphite (95%) was purchased from Strem Chemicals. Sodium azide was purchased from Matheson Coleman & Bell. 2-Nitropropane (96%) was purchased from Spectrum. Cupric acetate was purchased from Mallinckrodt. Copper sulfate (98%) was purchased from Strem Chemicals. 3-Bromo-1-trimethylsilyl-1-propyne (97%) was purchased from GFS Chemicals. Mercuric chloride (99.4%) was purchased from Baker. 2-Bromobenzyl alcohol was purchased from Combi-Blocks. Flash chromatography was performed using premium grade 60, 40-75 mesh silica gel from Sorbent Technology. Analytical thin layer chromatography (TLC) was carried out on Whatman silica gel plates (0.25 nm thick).

6.1.2 Instrumentation and Methods

^{1}H NMR spectra were recorded on either a Varian UNITY plus 500 MHz or INOVA 600 MHz spectrometer as noted in $CDCl_3$, and reported in parts per million (ppm) with TMS as an internal standard for the proton and the $CDCl_3$ triplet as an internal standard for carbon. FTIR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Low and high-resolution mass measurements were obtained on a benchtop Mariner electrospray ionization time-of-flight (ESITOF) mass

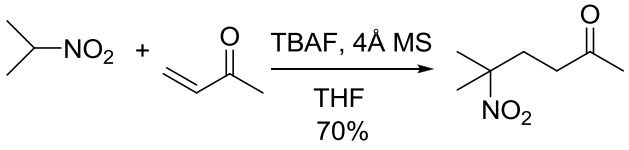
spectrometer. EPR measurements were performed on a Bruker X-band EPR spectrometer using 707-SQ EPR tubes (Wilmad) in anhydrous degassed toluene, except as noted. EPR settings were 20 mW for the microwave power and 1.0 G for the modulation width. Gel permeation chromatography (GPC) was performed using Waters apparatus equipped with five Styragel columns (300 x 4.6 mm, 5 μm bead size): HR 0.5 (pore size 50 Å, 0-1000 Da), HR 1 (pore size 100 Å, 100-5000 Da), HR 2 (pore size 500 Å, 500-20,000 Da), HR 4 (pore size 10,000 Å, 50-1,000,000 Da), HR 5E (linear bed, mixed pore sizes, 2000-4 x 10^6 Da). THF was used as the eluent at a flow rate of 0.35 mL/min at ambient temperature. A refractive index detector was used, and the molecular weights were calibrated against seven polystyrene standards ranging from 2000 to 156,000 Da. Absorption spectra were recorded on a Hewlett-Packard 8452A diode array spectrometer.

Fluorescence spectra were taken on a Perkin-Elmer LS 50B fluorescence spectrometer controlled by FL WinLab™ (version 2.0) software. Samples were placed in an open-sided 1 cm path length 10 x 10 mm quartz cuvette for both absorption and emission measurements. For the emission spectra of QDs taken at a series of quencher concentrations, after the addition of the quencher, the solution was shaken for 60 seconds before the emission spectrum was taken. Photoexcitation experiments were performed with a UVL-56 365-nm-wavelength hand-held TLC lamp. Photolysis of photocleavable nitroxides was performed with a 300 W reflector

lamp (Philips), a 300 W medium pressure mercury lamp, or a 200 W high pressure mercury lamp as noted. All fluorescence photos were taken under UV illumination produced by a UVGL-25 365-nm-wavelength hand-held TLC lamp. All spectroscopic studies were carried out at room temperature except as noted.

Nonlinear curve fitting was performed with either KaleidaGraph or OriginPro 8.0 programs. Bond lengths of nitroxide molecules were calculated from Molecular Mechanics calculations version 2 (MM2) embedded in Chem3D Ultra 8.0 software. All air- and moisture sensitive reactions were carried out under nitrogen atmosphere using oven-dried syringes and flame-dried glassware. Thin layer chromatography (TLC) visualization was performed with a UV lamp visualized at 254, nm and with *p*-anisaldehyde dip (PAA: 2.5 mL of *p*-anisaldehyde in 40 mL of 90:5:1 ethanol/concentrated sulfuric acid/glacial acetic acid) followed by heating.

6.2 Experimental Procedures for Chapter 3

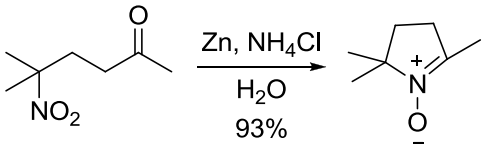


3.6

5-Methyl-5-nitrohexan-2-one (3.6). Following the procedure of Miller *et al*.,[3] to a solution of 2-nitropropane (4.20 mL, 45.3 mmol) and methyl vinyl ketone (4.20 mL, 49.0 mmol) with activated 4 Å molecular sieves in tetrahydrofuran (20 mL) was slowly added tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 20 mL, 20 mmol). The solution was allowed to stir overnight. The reaction mixture was filtered through a celite pad, and rinsed with dichloromethane. The filtrate was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 5.240 g of a brownish oil. The resulting oil was purified by flash column chromatography with 2:1 hexane/ethyl acetate to give 5.070 g (70% yield) of the title product as a non-viscous gold oil.

TLC: 2:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.41.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.45 (t, *J* = 7.8 Hz, 2H), 2.19 (t, *J* = 7.8 Hz, 2H), 2.16 (s, 3H), 1.58 (s, 6H) ppm.

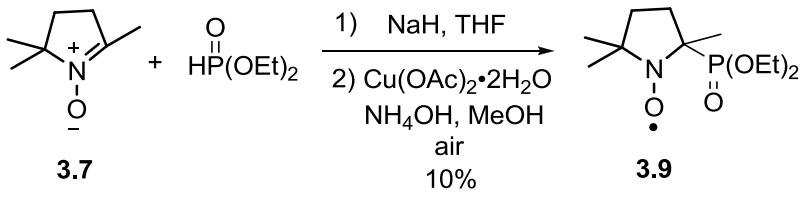


3.6 **3.7**

2-(2-Aminoethyl)-2,5,5-trimethylpyrrolidin-1-oxyl (3.7) Following the procedure of Delpierre and Lamchen,[4] to a solution of 5-methyl-5-nitrohexan-2-one (**3.6**, 2.453 g, 15.41 mmol) and ammonium chloride (864 mg, 16.2 mmol) in water (21 mL) chilled in an ice bath, was added zinc metal (4.093 g, 62.59 mmol) over 15 minutes. The solution was allowed to warm slowly to room temperature open to the atmosphere overnight. The reaction mixture was filtered through a celite pad, and rinsed with chloroform. The aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 1.826 g (93% yield) of the title product as a gold oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.59 (tq, *J* = 7.2, 1.2 Hz, 2H), 2.03 (t, *J* = 1.2 Hz, 3H), 2.00 (t, *J* = 7.2 Hz, 2H), 1.40 (s, 6H) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ 141.2, 73.2, 32.3, 29.1, 25.5, 13.2 ppm.



3.7 **3.9**

2,5,5-Trimethyl-2-diethylphosphite-pyrrolidin-*N*-oxyl (3.9). To a solution of diethyl phosphite (0.19 mL, 1.4 mmol) and sodium hydride (60% dispersion in mineral oil, 34 mg, 1.4 mmol) in tetrahydrofuran (2 mL) chilled in an ice bath, was added 3,4-dihydro-2,2,5-trimethyl-2*H*-pyrrole-1-oxide (**3.7**, 256 mg, 0.933 mmol) in tetrahydrofuran (2 mL). The solution was allowed to stir overnight, warming to room temperature. The next day, saturated ammonium chloride (5 mL) was added to quench the excess sodium hydride. The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was washed with brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in methanol (4.20 mL), and concentrated ammonium hydroxide solution (7.4 M, 0.30 mL, 2.2 mmol) was added. Cupric acetate (11 mg, 0.055 mmol) was added and air was bubbled through the solution for an hour. The solution turned blue immediately after adding the ammonium hydroxide. Afterwards, the mixture was concentrated *in vacuo*. Chloroform (10 mL), water (10 mL) and saturated sodium bisulfate (3 mL) were added to the reaction mixture. The aqueous layer was extracted with chloroform (2 × 10 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give

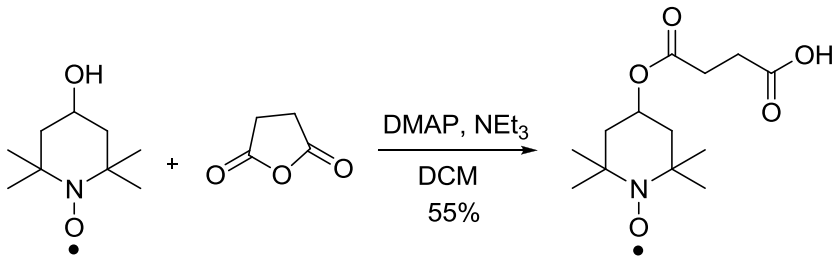
50 mg of a yellowish oil. The resulting oil was purified by silica gel column chromatography, first with 1:1 hexanes/ethyl acetate, then with 1:2 hexanes/ethyl acetate, and finally with 1:4 hexanes/ethyl acetate to give 25 mg (10% yield) of the title product as an orange oil.

TLC: 1:1 hexanes/ethyl acetate, UV, R_f = 0.25.

IR: ($CDCl_3$) 2978, 2933, 1244, 1050, 1023, 967 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 4.27-4.05 (m, 4H), 2.22 (m, 1H), 1.80 (m, 1H), 1.62 (m, 2H), 1.45 (d, J_{PH} = 17.4 Hz, 3H), 1.32 (m, 6H), 1.20 (s, 3H), 1.12 (s, 3H) ppm.

HRMS: M+1 (addition of $PhNHNH_2$, $C_{11}H_{25}NO_4P^+$) 266.1516 calcd; 266.1506 obsd.



3.10

4-(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yloxy)-4-oxobutanoic acid (3.10). Following the general procedure of Singh *et al*.,[5] to a solution of TEMPOL (200 mg, 1 mmol) and 4-dimethylaminopyridine (DMAP, 10 mg, 0.08 mmol) in dichloromethane (5 mL) cooled in an ice bath, was added triethylamine (0.90 mL, 6.5 mmol). A

solution of succinic anhydride (209 mg, 2.09 mmol) in dichloromethane (5 mL) was added slowly. The solution was allowed to warm to room temperature overnight. Water (10 mL) and 10% hydrochloric acid (3 mL) were added. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 190 mg of an orange oil. The resulting oil was purified by silica gel column chromatography with 1:2 hexanes/ethyl acetate to give 175 mg (55% yield) of the title product as an orange solid.

TLC: 1:2 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.40.

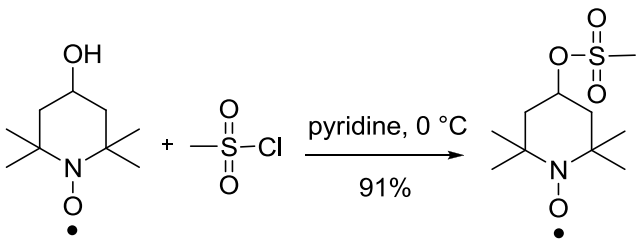
Melting point: 86-87 ^{o}C.

IR (neat): 2977, 1731, 1711, 1219, 1167 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 4.99 (m, 1H), 2.66 (t, *J* = 6.0 Hz, 2H), 2.48 (t, 6.0 Hz, 2H), 2.28 (dd, *J* = 12, 2.5 Hz, 2H), 1.94 (t, *J* = 12 Hz, 2H), 1.40 (s, 6H), 1.31 (s, 6H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 179.1 (C), 173.3 (C), 65.0 (CH), 60.8 (C), 41.9 (CH_2), 31.0 (CH_2), 30.5 (C), 28.1 (CH_3), 21.1 (CH_3) ppm.

HRMS: M+1 (addition of $PhNHNH_2$, $C_{13}H_{24}NO_5^+$) 274.1649 calcd; 274.1646 obsd.

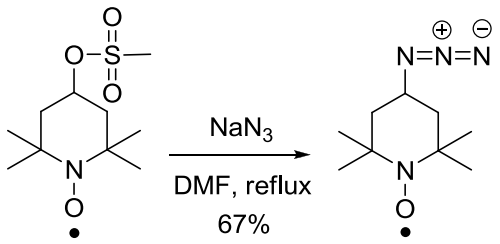


3.11

4-Methanesulfonyl-2,2,6,6-tetramethylpiperidin-*N*-oxyl (3.11). Following the procedure of Bushmakina *et al*.,[6] to an ice-cooled solution of 4-hydroxy-2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPOL, 2.008 g, 11.66 mmol) in pyridine (8.20 mL) was added methanesulfonyl chloride (1.80 mL, 23.1 mmol). The solution was allowed to warm to room temperature over 6 h, and then cold saturated sodium bicarbonate was added to the reaction mixture cooled over an ice bath. The solution was extracted with chloroform (4 × 40 mL). The combined organic layer was washed with saturated sodium bicarbonate (2 × 40 mL), and then with water (2 × 40 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 2.651 g (91% yield) of the title product as an orange solid.

Melting point: 85-87 ^{o}C.

^{1}H-NMR (500 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 4.94 (m, 1H), 3.01 (s, 3H), 2.08 (doublet of multiplet, *J* = 13 Hz, 2H), 1.80 (t, *J* = 13 Hz, 2H), 1.26 (s, 6H), 1.22 (s, 6H) ppm.

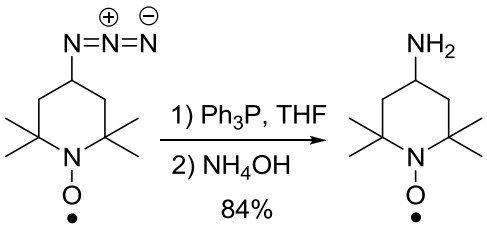


3.11 **3.12**

4-Azido-2,2,6,6-tetramethylpiperidin-*N*-oxyl (3.12). Following a modified procedure of Bushmakina *et al*.,[6] to a solution of 4-methanesulfonyl-2,2,6,6-tetramethylpiperidine-*N*-oxyl (**3.11**, 2.483 g, 9.918 mmol) in dimethylformamide (33 mL) was added sodium azide (1.290 g, 19.84 mmol). A condenser was attached, and the solution was heated at 110 ^{o}C overnight. Upon cooling, diethyl ether (200 mL) was added to the reaction mixture. The organic layer was washed with saturated sodium bicarbonate (100 mL) and water (4 × 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 1.312 g (67% yield) of the title product as an orange solid.

Melting point: 60-61 ^{o}C.

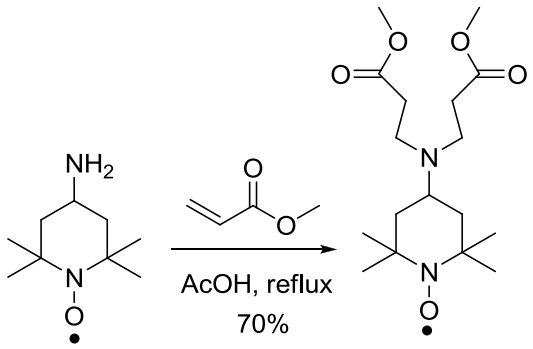
^{1}H-NMR (500 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 4.60 (m, 1H), 1.87 (doublet of multiplet, *J* = 12.6 Hz, 2H), 1.57 (t, *J* = 12.6 Hz, 2H), 1.23 (s, 6H), 1.16 (s, 6H) ppm.



3.12 **3.13**

4-Amino-2,2,6,6-tetramethylpiperidin-*N*-oxyl (3.13). Following a modified procedure of Bushmakina *et al*.,[6] to a solution of 4-azido-2,2,6,6-tetramethylpiperidin-*N*-oxyl (**3.12**, 490 mg, 2.48 mmol) in tetrahydrofuran (5.30 mL) was added triphenylphosphine (2.376 g, 8.968 mmol) in portions over 3 h. Concentrated ammonium hydroxide solution (7.4 M, 5.30 mL, 39 mmol) was then added. The solution was allowed to stir overnight. Solvent was removed *in vacuo* using only gentle heating (~40 ^{o}C). The residue was taken up in chloroform (50 mL), and extracted with 10% acetic acid (2 × 25 mL). The combined aqueous layer was neutralized with saturated sodium bicarbonate using a few drops of 2 M sodium hydroxide to make it slightly basic, extracted with chloroform (3 × 50 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 357 mg (84% yield) of the title product as an orange oil.

^{1}H-NMR (500 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 3.05 (m, 1H), 1.75 (doublet of multiplet, *J* = 12 Hz, 2H), 1.26 (t, *J* = 12 Hz, 2H), 1.17 (s, 6H), 1.14 (s, 6H) ppm.



3.13 **3.14**

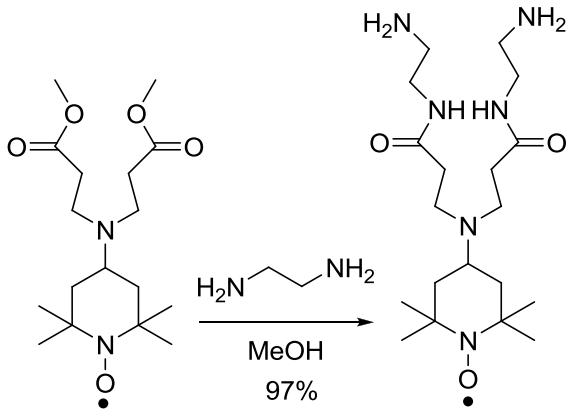
3,3′-(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl-amino)-*N*,*N*-bispropionic acid dimethyl ester (3.14). Following a modified procedure of Yao *et al*.,[7] to a solution of methyl acrylate (1.90 mL, 21.1 mmol) and glacial acetic acid (0.15 mL, 2.6 mmol) was added 4-amino-2,2,6,6-tetramethylpiperidin-*N*-oxyl (**3.13**, 357 mg, 2.08 mmol). The solution was allowed to stir overnight. Excess methyl acrylate was removed under reduced pressure. The residue was taken up in ethyl acetate (15 mL) and washed with saturated sodium bicarbonate (15 mL), water (15 mL), and brine (30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 504 mg (70% yield) of the title product as an orange oil.

IR: (neat) 2974, 2950, 1798, 1437, 1201, 1173 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 3.98 (t, *J* = 6.6 Hz, 1H), 3.66 (s, 6H), 2.79 (t, *J* = 6.6 Hz, 4H), 2.43 (t, *J* = 6.6 Hz, 4H), 1.64 (m, 2H), 1.45 (m, 2H), 1.24 (s, 6H), 1.19 (s, 6H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 173.1 (C), 59.4 (C), 51.6 (CH_3), 50.7 (CH), 46.3 (CH_2), 41.3 (CH_2), 34.8 (CH_2), 32.8 (CH_3), 20.0 (CH_3) ppm.

HRMS: M+1 (addition of $PhNHNH_2$, $C_{17}H_{33}N_2O_5^+$) 345.2384 calcd; 345.2367 obsd.



3.14 **3.15**

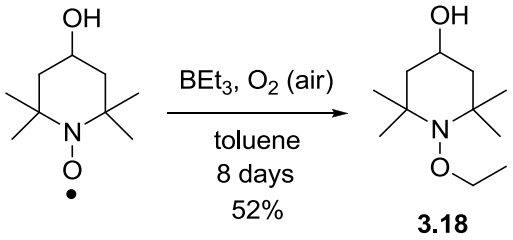
3,3′-(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl-azanediyl)bis(*N*-(2-aminoethyl)propanamide) (3.15). Following the general procedure of Yao *et al*.,[7] to a solution of 3,3′-(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl-amino) bispropionic acid dimethyl ester (482 mg, 1.40 mmol) in methanol (5.30 mL) was added ethylenediamine (9.50 mL, 140 mmol). The solution was allowed to stir at room temperature overnight. Excess ethylenediamine was removed *in vacuo* using toluene/methanol as an azeotrope[8] to give 540 mg (97% yield) of the title product as an orange oil.

IR: (neat) 3365, 2975, 2938, 1644, 1555, 1463, 1363 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 3.98 (t, *J* = 6.0 Hz, 1H), 3.29 (t, *J* = 6.0 Hz, 4H), 2.82 (t, 6.0 Hz, 4H), 2.76 (t, 4H, *J* = 6.0 Hz), 2.35 (t, *J* = 6.0 Hz, 4H), 1.48 (m, 4H), 1.16 (s, 6H), 1.11 (s, 6H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$, addition of $PhNHNH_2$): δ 172.9 (C), 59.2 (C), 50.2 (CH), 46.6 (CH_2), 42.0 (CH_2), 41.6 (CH_2), 40.7 (CH_2), 35.5 (CH_2), 33.0 (CH_3), 20.0 (CH_3) ppm.

HRMS: M+1 (addition of $PhNHNH_2$, $C_{19}H_{41}N_6O_3^+$) 401.3235 calcd; 401.3225 obsd.



3.18

1-Ethoxy-2,2,6,6-tetramethylpiperidin-4-ol (3.18). To a solution of TEMPOL (206 mg, 1.20 mmol) in toluene (4 mL) was added triethylborane (1.0 M in THF, 1.40 mL, 1.40 mmol). The solution was allowed to stir open to the atmosphere overnight. After five days, TEMPOL was not completely consumed, so more triethylborane (1.0 M in THF, 1.40 mL, 1.40 mmol) was added. The solution turned from orange to yellow within 15 minutes after the second addition of triethylborane. After eight days, the reaction mixture was concentrated *in vacuo* to give 151 mg of a yellowish oil. The resulting oil was purified by silica gel column chromatography, first with 10:1

hexanes/ethyl acetate, and then with 4:1 hexanes/ethyl acetate to afford 126 mg (52% yield) of the title product as a colorless oil.

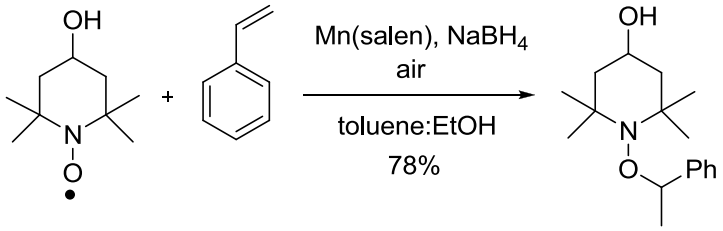
TLC: 10:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.64.

IR: (neat) 3267, 2972, 1372, 1360, 1040, 730 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.94 (m, 1H), 3.77 (q, *J* = 7.2 Hz, 2H), 1.80 (doublet of multiplet, 12 Hz, 2H), 1.44 (t, *J* = 12 Hz, 2H), 1.18 (s, 6H), 1.14 (s, 6H), 1.11 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C-NMR, DEPT (150 MHz, $CDCl_3$): δ 72.2 (CH_2), 63.8 (CH), 59.9 (C), 48.3 (CH_2), 33.4 (CH_3), 21.1 (CH_3), 13.8 (CH_3) ppm.

HRMS: M+1 ($C_{11}H_{24}NO_2^+$) 202.1802 calcd; 202.1766 obsd.



3.19

1-(1-Phenylethoxy)-2,2,6,6-tetramethylpiperidin-4-ol (3.19). Following a modified procedure of Hawker *et al*.,[9] TEMPOL (302 mg, 1.75 mmol) was dissolved in 2:3 v/v of toluene (6.40 mL) and ethanol (8.90 mL) followed by the addition of styrene (0.40 mL, 3.5 mmol). Manganese salen catalyst[1] (196 mg, 0.549 mmol) was added followed by sodium borohydride (198 mg, 5.23 mmol); the reaction was allowed to

stir open to the atmosphere overnight. The reaction mixture was concentrated *in vacuo* and taken up with dichloromethane (15 mL) and water (15 mL). The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layer was washed with saturated sodium bicarbonate (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 507 mg of a brownish oil. The resulting oil was purified by silica gel column chromatography, first with 4:1 hexanes/ethyl acetate, and then with 2:1 hexanes/ethyl acetate to give 379 mg (78% yield) of the title product as a white solid.

TLC: 4:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.23.

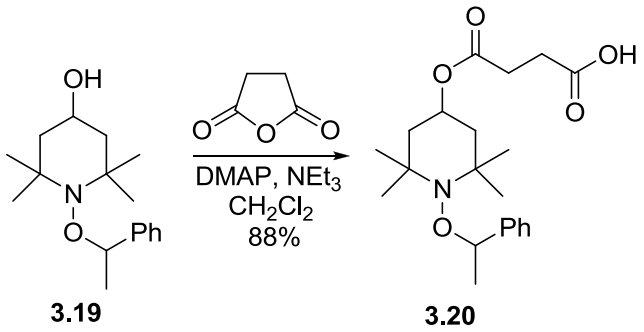
Melting point: 95-97 ^{o}C.

IR: (neat) 3286, 2969, 1449, 1373, 1361, 1043, 1031, 697 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.31-7.21 (m, 5H), 4.77 (q, *J* = 6.6 Hz, 1H), 3.93 (m, 1H), 1.84 (dt, *J* = 12.6, 3.6 Hz, 2H), 1.70 (dt, *J* = 12.6, 3.6 Hz, 2H), 1.48 (d, 6.6 Hz, 3H), 1.33 (s, 3H), 1.22 (s, 3H), 1.07 (s, 3H), 0.67 (s, 3H) ppm.

^{13}C-NMR, DEPT (150 MHz, $CDCl_3$): δ 145.4 (C), 128.0 (CH), 126.9 (CH), 126.6 (CH), 83.3 (CH), 63.3 (CH), 60.2 (C), 60.0 (C), 48.9 (CH_2), 48.8 (CH_2), 34.5 (CH_3), 34.2 (CH_3), 23.4 (CH_3), 21.3 (CH_3) ppm.

HRMS: M+1 ($C_{17}H_{28}NO_2^+$) 278.2115 calcd; 278.2114 obsd.



3.19 3.20

4-(1-Phenylethoxy-2,2,6,6-tetramethylpiperidin-4-yloxy)-4-oxobutanoic acid (3.20). Following the general procedure of Singh *et al*.,[5] to a solution of 1-(1-phenylethoxy)-2,2,6,6-tetrametylpiperidin-4-ol (355 mg, 1.28 mmol) and 4-dimethylaminopyridine (DMAP, 9.9 mg, 0.081 mmol) in dichloromethane (11 mL) was added triethylamine (0.90 mL, 6.46 mmol). Succinic anhydride (200 mg, 2 mmol) was added slowly while cooling the reaction mixture over an ice bath. The solution was allowed to warm to room temperature overnight. Water (15 mL) and 10% hydrochloric acid (5 mL) were added and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 516 mg of a golden-brown oil. The resulting oil was purified by silica gel column chromatography with 1:2 hexanes/ethyl acetate to give 425 mg (88% yield) of the title product as a slightly yellowish solid.

TLC: 1:2 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.78.

Melting point: 76-78 ^{o}C.

IR: (neat) 2975, 2934, 1734, 1714, 1363, 1174, 700 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.30-7.21 (m, 5H), 5.02 (m, 1H), 4.77 (q, *J* = 6.6 Hz, 1H), 2.64 (t, *J* = 6.6 Hz, 2H), 2.57 (t, *J* = 6.6 Hz, 2H), 1.86 (d, *J* = 12 Hz, 1H), 1.74 (doublet of multiplet, *J* = 12 Hz, 2H), 1.58 (t, *J* = 12 Hz, 1H), 1.48 (d, 6.6 Hz, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.66 (s, 3H) ppm.

^{13}C-NMR, DEPT (150 MHz, $CDCl_3$): δ 177.9 (C), 171.7 (C), 145.3 (C), 128.1 (CH), 127.0 (CH), 126.6 (CH), 83.4 (CH), 67.5 (CH), 61.3 (C), 60.2 (C), 44.5 (CH_2), 34.3 (CH_3), 34.0 (CH_3), 29.2 (CH_2), 29.0 (CH_2), 23.4 (CH_3), 21.1 (CH_3) ppm.

HRMS: M+1 ($C_{21}H_{32}NO_5^+$) 378.2275 calcd; 378.2276 obsd.

Synthesis of CdSe Quantum Dots. The synthesis of the CdSe QDs was based on the hot injection organometallic route described previously.[10] The synthesis was carried out by Abraham Wolcott. Standard air-free conditions were followed using a Schlenk line with nitrogen gas as the inert atmosphere. For the preparation of CdSe QDs, 2.29 g (5.92 mmol) of trioctylphosphine oxide (TOPO), 2.17 g (7.80 mmol) of tetradecylphosphonic acid (TDPA), 5.71 g (23.6 mmol) of hexadecylamine, and 500 mg (3.89 mmol) of cadmium oxide (CdO) were added to a 50 mL, three-neck flask equipped with a stir bar. The solids were heated to 130 °C under a flow of nitrogen with continuous stirring. At 130 °C, the solution was treated under vacuum at 30 mTorr to three successive degassing cycles on a nitrogen line over 1 h. The nitrogen flow was resumed, and the solution was heated. At 260 °C, the CdO-TDPA complex

formed, and the solution appeared optically clear with a slight yellowish tint. At 270 °C, 1.00 g (1.22 mL, 4.88 mmol) of tributylphosphine (TBP) was injected into the mixture with vigorous stirring. The temperature was lowered slightly and held at 260 °C. Selenium tributylphosphine (1.6 g, 20% by weight of Se in TBP) was injected into the mixture at 260 °C, and subsequent growth was monitored by UV-vis and photoluminescence spectrophotometry. Growth was stopped by the removal of the heating mantle after 4 min at 260 °C to give material exhibiting an excitonic peak at 576 nm, a band edge emission peak at 583 nm, and an emission full-width-half-maximum (fwhm) of 23 nm. The solution was allowed to cool to 60 °C, and 8 mL of anhydrous methanol was added to precipitate the CdSe QDs. Centrifugation was carried out at 3000 rpm, and the supernatant was discarded. To remove unreacted precursors, 6 mL of octanoic acid was added, and the mixture was sonicated and vortexed until the solution became optically clear. A minimum amount of anhydrous methanol was slowly added to precipitate the CdSe QDs. The resulting slightly opaque solution was centrifuged at 3000 rpm, and the supernatant was discarded. The CdSe solid was redissolved in anhydrous toluene and precipitated and decanted twice more; the CdSe QDs were then dried under a flow of nitrogen. The CdSe QD solids were dissolved in anhydrous toluene, and average size (D, nm) of the CdSe QDs were obtained from UV-visible absorption measurements following the

calibration **Equation 6.1** reported by Yu *et al*,[11] where λ (nm) is the wavelength of the first excitonic absorption peak of the quantum dots.

$$D = (1.6122 \times 10^{-9})\lambda^4 - (2.6575 \times 10^{-6})\lambda^3 + (1.6242 \times 10^{-3})\lambda^2 - (0.4277)\lambda + 41.57 \quad \textbf{Equation 6.1}$$

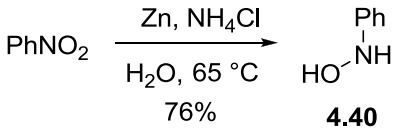
Concentrations (C, mol/L) of CdSe QDs were calculated using Lambert-Beer's law **Equation 6.2**, where A is the absorbance at the peak position of the first exciton absorption peak for the QDs, L is the path length (cm) of the radiation beam used for recording the absorption spectrum. ε is the extinction coefficient per mole of particles, which was obtained from the calibration **Equation 6.3** reported by Yu *et al*,[11] where ΔE (eV) is the transition energy corresponding to the first absorption peak.

$$A = \varepsilon CL \quad \textbf{Equation 6.2}$$

$$\varepsilon = 5857\ (D)^{2.65} \quad \textbf{Equation 6.3}$$

The standard deviation of the extinction coefficient values (ε) reported by these authors for QDs is ±15%; thus all the QD concentrations reported in this work are affected by this uncertainty. The low (23 nm) fwhm of the 583 nm emission indicates that the samples were of narrow size distribution.

6.3 Experimental Procedures for Chapter 4

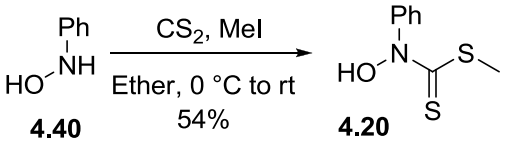


4.40

***N*-Phenylhydroxylamine (4.40).** Following the procedure of Renaud *et al*.,[12] zinc powder (3.485 g, 53.28 mmol) was added slowly in portions to a solution of ammonium chloride (1.555 g, 29.06 mmol) and nitrobenzene (2.60 mL, 24.8 mmol) in water (24 mL) under vigorous stirring, while maintaining the temperature below 65 °C. The solution was allowed to stir at room temperature open to atmosphere overnight. The reaction mixture was filtered through celite, and the filter-cake was rinsed with dichloromethane and methanol. The filtrate was extracted with dichloromethane (2 × 20 mL). The organic layers were combined and concentrated *in vacuo* to approximately 10 mL in volume. The title product was obtained as a wool-like white solid (2.005 g, 76% yield) after several precipitations from the organic layer at -78 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 2H), 6.98 (m, 3H), 6.79 (br s, 1H), 5.96 (br s, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 149.9, 129.1, 122.5, 114.8 ppm.

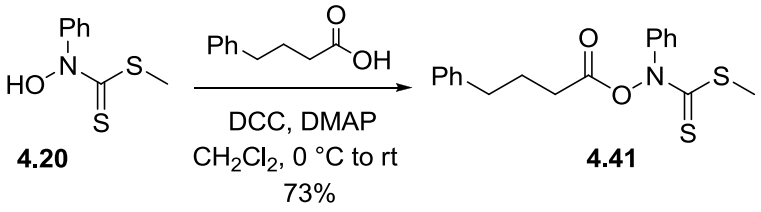


4.40 **4.20**

***N*-Hydroxy-*S*-methyl-*N*-phenyldithiocarbamate (4.20).** Following the procedure of Renaud *et al.*,[12] carbon disulfide (0.91 mL, 15 mmol) and iodomethane (0.95 mL, 15 mmol) were added at 0 °C to a solution of *N*-phenylhydroxylamine (**4.40**, 1.500 g, 13.75 mmol) in diethyl ether (60 mL). Triethylamine (9.60 mL, 68.8 mmol) was added dropwise. The solution was allowed to warm to room temperature overnight. The reaction mixture was extracted with 5% aqueous sodium bicarbonate (2 × 25 mL). The aqueous layer was acidified to pH 3 with concentrated hydrochloric acid, and extracted with diethyl ether (2 × 50 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 1.4808 g (54% yield) of the title product as a yellow-white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 10.8 (br s, 1H), 7.48 (m, 5H), 2.62 (s, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 186.3, 130.6, 129.6, 129.3, 126.8, 124.3, 19.7 ppm.



Methyl 4-phenylbutanoyloxy(phenyl)carbamodithioate (4.41). Following the general procedure of Renaud *et al*.,[12] to a solution of 4-phenylbutyric acid (381 mg, 2.30 mmol) in dichloromethane (20 mL) was added 1,3-dicyclohexylcarbodiimide (DCC, 528 mg, 2.53 mmol) and 4-dimethylaminopyridine (DMAP, 42 mg, 0.34 mmol) at 0 °C, and the reaction mixture was stirred for 30 minutes. The flask was covered with aluminum foil, and a solution of *N*-hydroxy-*S*-methyl-*N*-phenyldithiocarbamate (**4.20**, 426 mg, 2.14 mmol) in dichloromethane (4 mL) was added slowly at 0 °C. The mixture was stirred overnight at room temperature, and then concentrated *in vacuo* to give 654 mg of a yellowish oil. The oil was purified by silica gel column chromatography with 4:1 hexanes/ethyl acetate to give 540 mg (73% yield) of the title product as a yellowish oil.

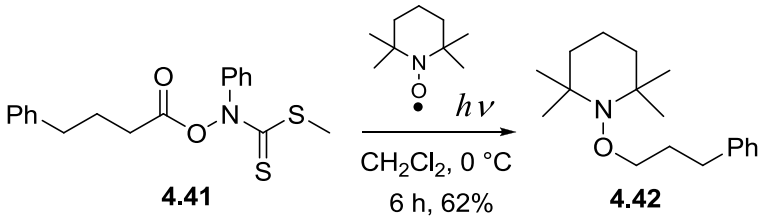
TLC: 4:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.56.

IR: ($CDCl_3$) 3026, 2922, 1796, 1579, 1489, 1360, 1072, 694 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.57-7.12 (m, 5H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.60 (s, 3H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.04 (tt, *J* = 7.5 Hz, 2H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 197.8 (C), 170.0 (C), 141.4 (C), 140.9 (C), 130.2 (CH), 129.8 (CH), 128.7 (CH), 128.4 (CH), 126.4 (CH), 35.0 (CH_2), 30.9 (CH_2), 26.2 (CH_2), 19.5 (CH_3) ppm.

HRMS: M+1 ($C_{18}H_{20}NO_2S_2^+$) 346.0930 calcd; 346.1009 obsd.



1-(3-Phenylpropoxy)-2,2,6,6-tetramethylpiperidine (4.42). Following a modified procedure of Renaud *et al*.,[12] a solution of methyl 4-phenylbutanoyloxy(phenyl)carbamodithioate (**4.41**, 100 mg, 0.3 mmol) in degassed dichlorometane (2 mL) was added slowly to a solution of TEMPO (51 mg, 0.32 mmol) in dichlorometane (1.50 mL). The solution was irradiated with a 300 W medium pressure mercury lamp under nitrogen at 0 °C for 6 hours. The reaction mixture was concentrated *in vacuo* to give 62 mg of an orange oil. The oil was purified by silica gel column chromatography with 20:1 hexanes/ethyl acetate to give 50 mg (62% yield) of the title product as a yellowish oil.

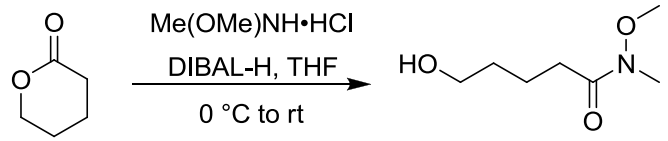
TLC: 20:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.70.

IR: ($CDCl_3$) 3026, 2931, 2108, 1574, 696 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30-7.17 (m, 5H), 3.77 (t, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 1.86 (tt, *J* = 6.5 Hz, 2H), 1.70-1.26 (m, 6H), 1.14 (s, 6H), 1.11 (s, 6H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 142.6 (C), 128.6 (CH), 128.5 (CH), 125.9 (CH), 76.3 (CH_2), 59.9, (C), 39.8 (CH_2), 33.0 (CH_2), 30.7 (CH_2), 25.4 (CH_3), 20.3 (CH_3), 17.4 (CH_2) ppm.

HRMS: M+1 ($C_{18}H_{30}NO^{+}$) 276.2322 calcd; 276.2317 obsd.



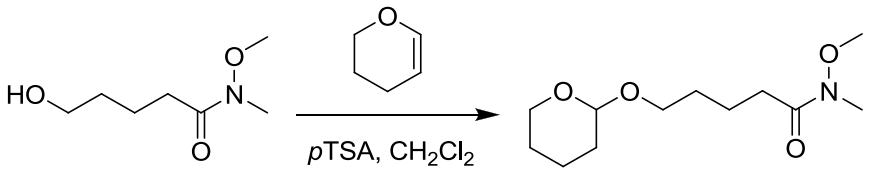
4.47

5-Hydroxy-*N*-methoxy-*N*-methylpentanamide (4.47).[13] Following the general procedure of Huang *et al*.,[14] a solution of DIBAL-H (1.0 M in hexanes, 183 mL, 183 mmol) was added to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (17.806 g, 182.53 mmol) in tetrahydrofuran (20 mL) at 0 °C. The mixture was allowed to warm to room temperature for two hours. This solution was added slowly to a solution of δ-valerolactone (14 mL, 152 mmol) in tetrahydrofuran (600 mL) at room temperature. The solution was allowed to warm to room temperature overnight. The reaction was cooled to 0 °C, and then quenched with water (100 mL) and saturated sodium bisulfate (130 mL). The mixture was extracted with dichloromethane (5 × 100 mL). The combined organic layer was washed with brine,

dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 18.724 g (76% yield) of the title compound as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.63 (t, *J* = 7.0 Hz, 2H), 3.18 (s, 3H), 2.47 (t, *J* = 7.0 Hz, 2H), 2.16 (br s, 1H), 1.73 (m, 2H), 1.61 (m, 2H) ppm.

^{13}C NMR, DEPT (125 MHz, C_6D_6): δ 175.0 (C), 62.3 (CH_2), 60.9 (CH_3), 33.1 (CH_2), 32.4 (CH_3), 32.0 (CH_2), 21.4 (CH_2) ppm.



4.47 **4.48**

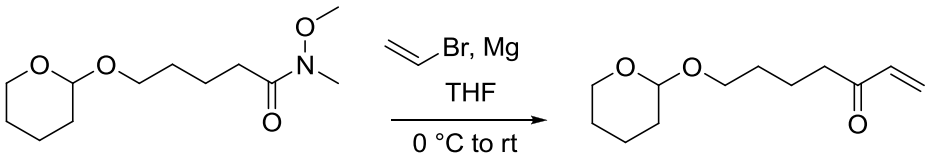
***N*-Methoxy-*N*-methyl-5-(tetrahydro-2*H*-pyran-2-yloxy) pentanamide (4.48).**[13] Following a modified procedure of Ryu and Jeong,[13] to a solution of 5-hydroxy-*N*-methoxy-*N*-methylpentanamide (**4.47**, 18.724 g, 116.16 mmol) and 3,4-dihydro-2*H*-pyran (12 mL, 130 mmol) in dichloromethane (232 mL) was added *p*-toluenesulfonic acid monohydrate (225 mg, 1.17 mmol). The reaction mixture was allowed to stir at room temperature overnight. The mixture was quenched with saturated sodium bicarbonate (60 mL). The aqueous layer was extracted with dichloromethane (3 × 60 mL). The combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 10.657 g of a slightly yellowish oil. The oil

was purified by silica gel column chromatography with 1:1 hexanes/ethyl acetate to give 9.0645 g (68% yield) of the title compound as a colorless oil.

TLC: 1:1 hexanes:ethyl acetate, *p*-anisaldehyde stain, R_f = 0.36.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.57 (t, *J* = 4.5 Hz, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 3.67 (s, 3H), 3.48 (m, 1H), 3.39 (m, 1H), 3.16 (s, 3H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.84-1.48 (m, 10H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$): δ 174.7 (C), 99.0 (CH), 67.4 (CH_2), 62.4 (CH_2), 61.4 (CH_3), 32.3 (CH_3), 31.8 (CH_2), 30.9 (CH_2), 29.6 (CH_2), 25.7 (CH_2), 21.6 (CH_2), 19.8 (CH_2) ppm.



4.48 **4.49**

7-(Tetrahydro-2*H*-pyran-2-yloxy) hept-1-en-3-one (4.49).[13] Vinylmagnesium bromide was prepared from the reaction of vinyl bromide (1 M in THF, 118 mL, 118 mmol) and magnesium turnings (2.840 g, 117 mmol). Iodine was added, and a heat from heat gun was carefully applied to accelerate the reaction. The Grignard solution was added slowly to a solution of *N*-methoxy-*N*-methyl-5-(tetrahydro-2*H*-pyran-2-yloxy) pentanamide (**4.48**, 14.329 g, 58.409 mmol) in tetrahydrofuran (110 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature

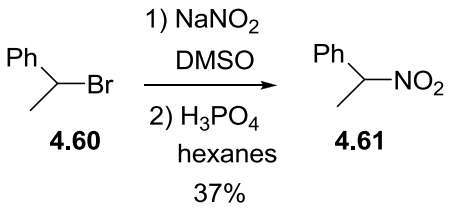
overnight. The next day, the reaction was cooled to 0 °C, and then quenched with saturated ammonium chloride (200 mL). Water was added to dissolve the white precipitate, and a spatula tip of hydroquinone was added to prevent the polymerization of the product. The aqueous layer was extracted with dichloromethane (2 × 200 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 10.829 g of an orange oil. The oil was purified by silica gel column chromatography with 4:1 hexanes/ethyl acetate to give 7.3948 g (60% yield) of the title compound as a colorless oil.

TLC: 4:1 hexane:ethyl acetate, *p*-anisaldehyde stain, R_f = 0.45.

IR ($CDCl_3$): 2942, 2870, 1700, 1682, 1402, 1034 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.34 (dd, *J* = 10.5, 17.5 Hz, 1H), 6.21 (d, *J* = 1.5, 17.5 Hz, 1H), 5.81 (d, *J* = 1.5, 10.5 Hz, 1H), 4.56 (t, *J* = 3.5 Hz, 1H), 3.84 (m, 1H), 3.74 (m, 1H), 3.48 (m, 1H), 3.39 (m, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 1.83-1.48 (m, 10 H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$): δ 200.9 (C), 136.8 (CH), 128.1 (CH_2), 99.0 (CH), 67.3 (CH_2), 62.5 (CH_2), 39.5 (CH_2), 30.9 (CH_2), 29.4 (CH_2), 25.6 (CH_2), 21.0 (CH_2), 19.8 (CH_2) ppm.

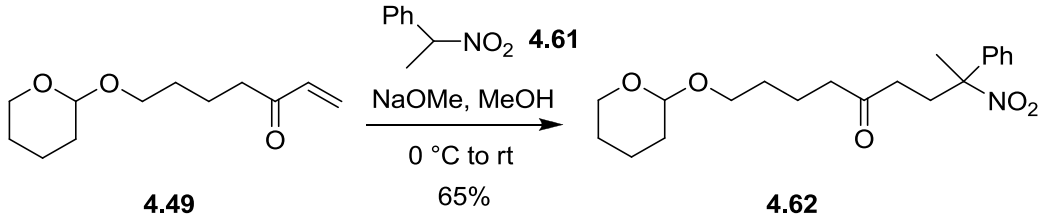


4.60 **4.61**

(1-Nitroethyl)benzene (4.61).[15] Following the procedure of Kornblum and Wade,[15] (1-bromoethyl)benzene (**4.60**, 8 mL, 57 mmol) was added to a solution of sodium nitrite (7.897 g, 113.7 mmol) in dimethyl sulfoxide (91 mL) cooled in a water bath. The solution turned from slightly yellow to green in color within five minutes. The reaction mixture was stirred for 20 minutes, while protected from light with aluminum foil. The mixture was taken up with diethyl ether (20 mL) and water (20 mL). The aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 6.125 g of a golden-olive oil. The resulting oil was dissolved in 21.5 mL of hexanes and vigorously stirred for 75 minutes with 17 mL of 85% *o*-phosphoric acid, and the phases separated. This treatment was repeated a total of three times; and the reaction flask was covered with aluminum foil the entire time. The hexanes layer was then washed with water (2 × 10 mL), brine (10 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 5.008 g of a yellowish oil. The oil was purified by distillation using Kugelrohr (T = 65 °C, P = 2 atm) to give 3.150 g (37% yield) of the title product as a yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (m, 5H), 5.63 (q, *J* = 7.5 Hz, 1H), 1.90 (d, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$): δ 135.8 (C), 129.9 (CH), 129.2 (CH), 127.6 (CH), 86.4 (CH), 19.6 (CH_3) ppm.



8-Nitro-8-phenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)nonan-5-one (4.62). To a solution of (1-nitroethyl)benzene (**4.61**) (2.275 g, 15.05 mmol) in methanol (49 mL) chilled in an ice bath, was added sodium methoxide (896 mg, 16.6 mmol). The solution was stirred for 15 minutes. 7-(Tetrahydro-2*H*-pyran-2-yloxy)hept-1-en-3-one (**4.49**, 3.043 g, 14.33 mmol) in methanol (20 mL) was added. The mixture was allowed to warm to room temperature overnight. To quench the reaction, saturated bisulfate was added until pH~7. The reaction mixture was concentrated *in vacuo*, and taken up with ethyl acetate (100 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 35 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 3.587 g of a yellowish

oil. The oil was purified by silica gel column chromatography with 2:1 hexanes/ethyl acetate to give 3.408 g (65% yield) of the title compound as a yellowish oil.

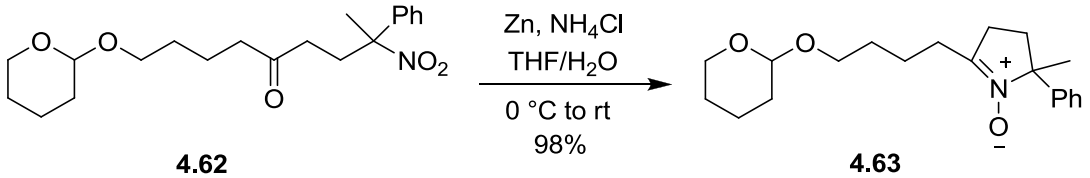
TLC: 2:1 hexane:ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.45.

IR ($CDCl_3$): 2944, 2871, 1715, 1541, 1032, 910, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.35 (m, 5H), 4.56 (t, *J* = 2.5 Hz, 1H), 3.85 (m, 1H), 3.73 (m, 1H), 3.49 (m, 1H), 3.37 (m, 1H), 2.72 (m, 1H), 2.61 (m, 1H), 2.40 (m, 4H), 1.93 (s, 3H), 1.84-1.51 (m, 10H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$): δ 208.7 (C), 139.5 (C), 129.1 (CH), 125.5 (CH), 99.1 (CH), 93.0 (C), 67.3 (CH_2), 62.6 (CH_2), 42.8 (CH_2), 37.9 (CH_2), 33.3 (CH_2), 30.9 (CH_2), 29.3 (CH_2), 25.6 (CH_2), 24.6 (CH_3), 20.8 (CH_2), 19.9 (CH_2) ppm.

HRMS: M+1 ($C_{20}H_{30}NO_5^+$) 364.2118 calcd; 364.2124 obsd.



4.62 **4.63**

2-Methyl-2-phenyl-5-(4-(tetrahydro-2*H*-pyran-2-yloxy)butyl)-3,4-dihydro-2*H*-pyrrole-1-oxide (4.63). To a solution of 8-nitro-8-phenyl-1-(tetrahydro-2*H*-pyran-2-yloxy) nonan-5-one (**4.62**) (3.037 g, 8.356 mmol) and ammonium chloride (492 mg, 9.19 mmol) in tetrahydrofuran (42 mL) and water (14 mL) was added zinc powder (2.186 g, 33.42 mmol) at 0 °C over 15 minutes. The reaction mixture was allowed to

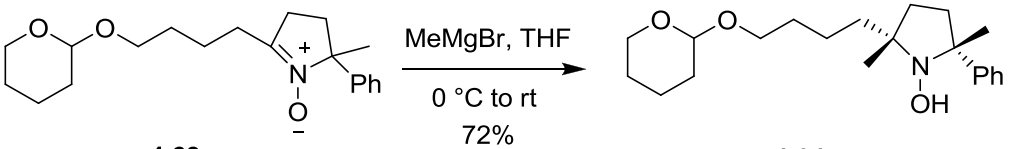
warm to room temperature open to the atmosphere overnight. The mixture was filtered through a celite pad, and rinsed with ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 2.719 g (98% yield) of the title compound as a slightly yellowish oil. The compound was used in the next step without purification.

IR ($CDCl_3$): 2940, 2868, 1590, 1445, 1032, 765, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.41-7.25 (m, 5H), 4.58 (t, *J* = 2.5 Hz, 1H), 3.86 (m, 1H), 3.79 (m, 1H), 3.50 (m, 1H), 3.45 (m, 1H), 2.72-2.56 (m, 4H), 2.40 (m, 1H), 2.22 (m, 1H), 1.84 (s, 3H), 1.83-1.50 (m, 10H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$): δ 147.3 (C), 142.5 (C), 128.8 (CH), 127.5 (CH), 125.4 (CH), 99.2 (CH), 79.5 (C), 67.2 (CH_2), 62.7 (CH_2), 35.5 (CH_2), 30.9 (CH_2), 29.9 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 25.7 (CH_3), 25.6 (CH_2), 22.2 (CH_2), 19.9 (CH_2) ppm.

HRMS: M+1 ($C_{20}H_{30}NO_3^+$) 332.2220 calcd; 332.2228 obsd.



4.63 **4.64**

2,5-Dimethyl-2-phenyl-5-(4-(tetrahydro-2H-pyran-2-yloxy)butyl)pyrrolidin-1-ol (4.64). To a solution of 2-methyl-2-phenyl-5-(4-(tetrahydro-2*H*-pyran-2-yloxy)butyl)-

3,4-dihydro-2*H*-pyrrole-1-oxide (**4.63**, 2.700 g, 8.146 mmol) in tetrahydrofuran (27 mL) was slowly added a solution of methylmagnesium bromide (1 M in THF, 49 mL, 49 mmol) at 0 °C. The ice bath was removed, and the reaction mixture was allowed to stir at room temperature overnight. The reaction was cooled to 0 °C, and then quenched with saturated ammonium chloride (50 mL). The mixture was diluted with ethyl acetate (60 mL) and H_2O (60 mL). The aqueous layer was extracted with ethyl acetate (2 × 60 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 2.575 g of a yellowish oil. The oil was purified by silica gel column chromatography with 2:1 hexanes/ethyl acetate to give 2.038 g (72% yield) of the title compound as an orange oil.

TLC: 2:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.65.

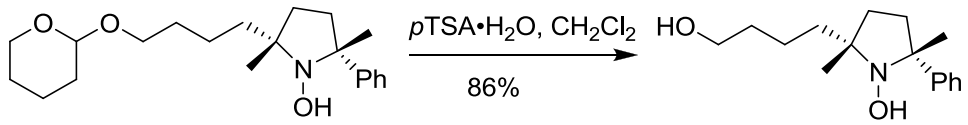
IR ($CDCl_3$): 2942, 2869, 1444, 1264, 1135, 1033, 736, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.61 (m, 2H), 7.37 (m, 2H), 7.25 (m, 1H), 4.64 (m, 1H), 3.95-3.83 (m, 2H), 3.56-3.47 (m, 2H), 2.04-1.57 (m, 16H), 1.62 (s, 3H), 1.31 (s, 3H) ppm.

^{13}C NMR, DEPT (150 MHz, $CDCl_3$, two diastereomers): δ 149.6 (C), 149.5 (C), 127.4 (CH), 125.34 (CH), 125.30 (CH), 125.2 (CH), 125.1 (CH), 98.6 (CH), 98.3 (CH), 67.7 (C), 67.5 (C), 67.0 (CH_2), 66.7 (CH_2), 64.6 (C), 62.1 (CH_2), 61.8 (CH_2), 42.2 (CH_2), 41.5 (CH_2), 37.2 (CH_2), 37.1 (CH_2), 32.5 (CH_2), 32.2 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.5

(CH_2), 24.9 (CH_2), 21.6 (CH_3), 21.3 (CH_3), 20.8 (CH_2), 20.3 (CH_2), 19.4 (CH_2), 19.1 (CH_2) ppm.

HRMS: M+1 ($C_{21}H_{34}NO_3^+$) 348.2533 calcd; 348.2541 obsd.



4.64 **4.65**

2-(4-Hydroxybutyl)-2,5-dimethyl-5-phenylpyrrolidin-1-ol (4.65). To a solution of 2,5-dimethyl-2-phenyl-5-(4-(tetrahydro-2H-pyran-2-yloxy)butyl)pyrrolidin-1-ol (**4.64**, 960 mg, 2.76 mmol) in tetrahydrofuran (45 mL) and MeOH (26 mL) was added *p*-toluenesulfonic acid monohydrate (53 mg, 0.28 mmol). The reaction mixture was allowed to stir at room temperature overnight. Solid sodium bicarbonate was added until pH~7. The mixture was filtered, and concentrated *in vacuo* to give 750 mg of a yellowish oil. The oil was purified by silica gel column chromatography with 1:2 hexanes/ethyl acetate to give 626 mg (86% yield) of the title compound as an orange oil.

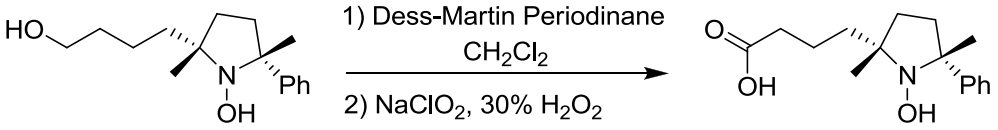
TLC: 1:2 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.49.

IR ($CDCl_3$): 3419 (br), 2975, 2868, 1445, 1367, 1216, 760, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, addition of phenylhydrazine): δ 7.94-6.97 (br m, 5H), 4.50-3.76 (br m, 2H), 2.63-1.45 (br m, 10H), 1.72 (s, 3H), 1.42 (s, 3H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$, addition of phenylhydrazine): δ 147.7 (C), 126.1 (CH), 124.1 (CH), 123.8 (CH), 66.6 (C), 63.6 (C), 60.9 (CH_2), 40.6 (CH_2), 35.5 (CH_2), 32.2 (CH_2), 31.5 (CH_2), 20.0 (CH_3), 19.9 (CH_3), 18.9 (CH_2).

HRMS: M+1 ($C_{16}H_{26}NO_2^+$) 264.1958 calcd; 264.1962 obsd.



4.65 **4.66**

4-(1-Hydroxy-2,5-dimethyl-5-phenylpyrrolidin-2-yl)butanoic acid (4.66). To a solution of 2-(4-hydroxybutyl)-2,5-dimethyl-5-phenylpyrrolidin-1-ol (**4.65**, 464 mg, 1.76 mmol) in dichloromethane (26 mL) was added Dess-Martin periodinane[2] (1.494 g, 3.522 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The next day, the mixture was filtered through a celite pad, and rinsed with dichloromethane. The filtrate was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 521 mg of an orange oil. The oil was suspended in acetonitrile (2 mL) and water (2 mL). Sodium phosphate (57 mg, 0.48 mmol) and hydrogen peroxide (30% in water, 210 μL, 1.8 mmol) were added. The mixture was cooled in an ice bath before a solution of sodium chlorite (278 mg, 2.46 mmol) in water (3 mL) was added slowly. The reaction mixture was allowed to warm to room temperature overnight

open to the atmosphere. The next day, 10% hydrochloric acid was added dropwise to adjust the pH to 1. The solution was taken up with dichloromethane (5 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 455 mg of a yellowish oil. The oil was purified by silica gel column chromatography with 1:1 hexanes/ethyl acetate to give 239 mg (49% yield) of the title compound as an orange oil.

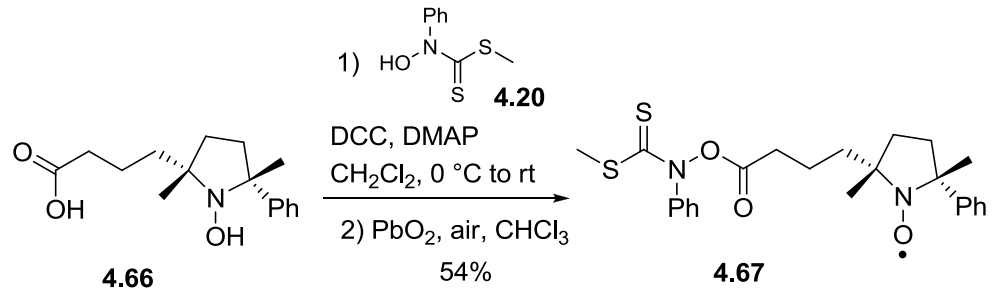
TLC: 1:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.49.

IR ($CDCl_3$): 3459 (br), 2974, 1732, 1708, 1411, 1261, 764, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, addition of phenylhydrazine): δ 10.27 (br s, 1H), 7.69-6.86 (br m, 5H), 2.68-1.16 (br m, 10H), 1.71 (s, 3H), 1.44 (s, 3H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$, addition of phenylhydrazine): δ 177.6 (C), 139.7 (C), 127.8 (CH), 127.7 (CH), 73.0 (C), 72.8 (C), 37.3 (CH_2), 34.4 (CH_2), 32.4 (CH_2), 31.1 (CH_2), 22.3 (CH_3), 21.3 (CH_3), 19.9 (CH_2).

HRMS: M+1 ($C_{16}H_{24}NO_3^+$) 278.1751 calcd; 264.1761 obsd.



Methyl-4-(*N*-oxyl-2,5-dimethyl-5-phenylpyrrolidin-2-yl)butanoyloxy(phenyl) carbamodithioate (**4.67**). Following the general procedure of Renaud *et al*.,[12] 4-(1-hydroxy-2,5-dimethyl-5-phenylpyrrolidin-2-yl)butanoic acid (**4.66**, 226 mg, 0.814 mmol) was added to a solution of 1,3-dicyclohexylcarbodiimide (DCC, 204 mg, 0.989 mmol) and 4-dimethylaminopyridine (DMAP, 10 mg, 0.08 mmol) in dichloromethane (13.60 mL) at 0 °C, and the reaction mixture was stirred for 30 minutes. The flask was covered with aluminum foil, and a solution of methyl hydroxyl (phenyl) carbamodithioate (**4.20**, 179 mg, 0.898 mmol) in dichloromethane (4.50 mL) was added slowly at 0 °C. The mixture was stirred overnight at room temperature, and then concentrated *in vacuo* to give 370 mg of a yellowish oil. The oil was purified by silica gel column chromatography with 4:1 hexanes/ethyl acetate to give 200 mg (52% yield) of the title product as an orange oil.

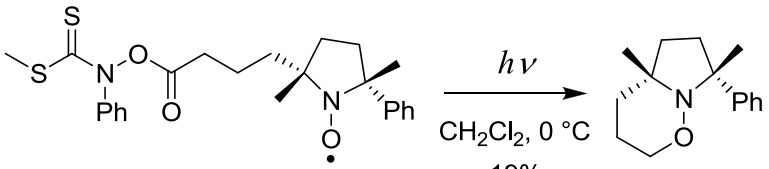
TLC: 4:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.26.

IR: ($CDCl_3$) 2973, 2919, 1796, 1366, 1074, 759, 697 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$, addition of phenylhydrazine, two rotamers): δ 7.62-6.84 (m, 15H), 3.27 (td, 2H, *J* = 2.5, 12.5 Hz), 2.64 (s, 3H), 2.62 (s, 3H), 2.56-1.50 (m, 8H), 1.68 (s, 3H), 1.59 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$, addition of phenylhydrazine): δ 197.7 (C), 170.2 (C), 141.4 (C), 136.9 (C), 130.1 (CH), 129.5 (CH), 129.4 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.7 (CH), 126.6 (CH), 126.1 (CH), 125.7 (CH), 125.6 (CH), 69.9 (C), 68.6 (C), 65.3 (C), 64.6 (C), 42.4 (CH_2), 41.8 (CH_2), 37.5 (CH_2), 37.5 (CH_2), 36.7 (CH_2), 36.5 (CH_2), 34.9 (CH_2), 32.9 (CH_2), 32.0 (CH_2), 22.1 (CH_3), 22.0 (CH_3), 21.6 (CH_3), 21.5(CH_3), 19.9 (CH_2), 19.7 (CH_2), 19.6 (CH_3), 19.4 (CH_3) ppm.

HRMS: M+1 ($C_{24}H_{31}N_2O_3S_2^+$, addition of phenylhydrazine) 459.1771 calcd; 459.1775 obsd.



4.67 **4.68**

4,7-Dimethyl-7-phenylhexahydro-*2H*-pyrrolo[1,2]oxazine (4.68). Following a modified procedure of Renaud *et al*.,[12] a solution of methyl-4-(*N*-oxyl-2,5-dimethyl-5-phenylpyrrolidin-2-yl)butanoyloxy(phenyl) carbamodithioate (**4.67**, 155 mg, 0.338 mmol) in dichlorometane (11 mL) was irradiated with a 300 W medium pressure mercury lamp under nitrogen at 0 °C for 2 hours. The reaction mixture was

concentrated *in vacuo* to give 121 mg of a slightly yellowish oil. The oil was purified by silica gel column chromatography with 20:1 hexanes/ethyl acetate to give 15 mg (19% yield) of the title product as a slightly yellowish oil.

TLC: 20:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.71.

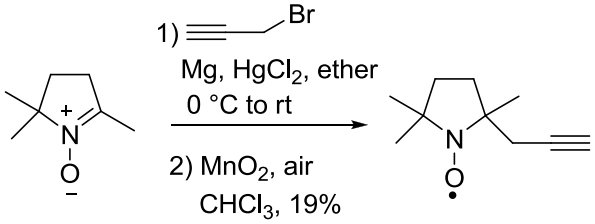
IR: ($CDCl_3$) 2939, 1579, 1444, 1054, 762, 699 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.31 (m, 2H), 7.18 (m, 1H), 4.09 (m, 2H), 2.18 (m, 1H), 2.04 (m, 1H), 1.94 (m, 2H), 1.80 (m, 1H), 1.73 (m, 1H), 1.67 (m, 1H), 1.51-1.45 (m, 2H), 1.49 (s, 3H), 1.33 (s, 3H) ppm.

^{13}C-NMR, DEPT (150 MHz, $CDCl_3$): δ 151.9 (C), 127.7 (CH), 125.5 (CH), 70.9 (CH_2), 64.9 (C), 61.3 (C), 39.1 (CH_2), 37.8 (CH_2), 34.3 (CH_2), 29.7 (CH_2), 25.8 (CH_3), 21.8 (CH_2), 17.3 (CH_3) ppm.

See appendix for 2D NMR spectra.

HRMS: M+1 ($C_{15}H_{22}NO^+$) 232.1696 calcd; 276.1702 obsd.



4.44 **4.73**

2,2,5-Trimethyl-5-(prop-2-ynyl)pyrrolidin-*N*-oxyl (4.73).[16] Magnesium turnings (194 mg, 7.98 mmol) and mercuric chloride (43 mg, 0.16 mmol) were vigorously stirred in

diethyl ether (16 mL) at room temperature for 30 minutes. The solution turned grey and propargyl bromide (0.60 mL, 7.7 mmol) was added. Propargylmagnesium bromide was formed after stirring at room temperature for 35 minutes, and was allowed to stir for the next two hours. The resulting Grignard solution was added slowly to a solution of 3,4-dihydro-2,2,5-trimethyl-2H-pyrrole-1-oxide (**4.44**, 500 mg, 4 mmol) in diethyl ether (1 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature overnight. The next day, the reaction was cooled to 0 °C, and then quenched with saturated ammonium chloride (20 mL). The reaction mixture was taken up with diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give an orange oil. The oil was dissolved in chloroform (13 mL), and manganese dioxide (171 mg, 1.97 mmol) was added. Air was bubbled through the solution for an hour. The mixture was filtered through a celite pad, and rinsed with chloroform. The filtrate was concentrated *in vacuo* to give 205 mg of an orange oil. The oil was purified by silica gel column chromatography with 4:1 hexanes/ethyl acetate to give 126 mg (19% yield) of the title compound as an orange solid.

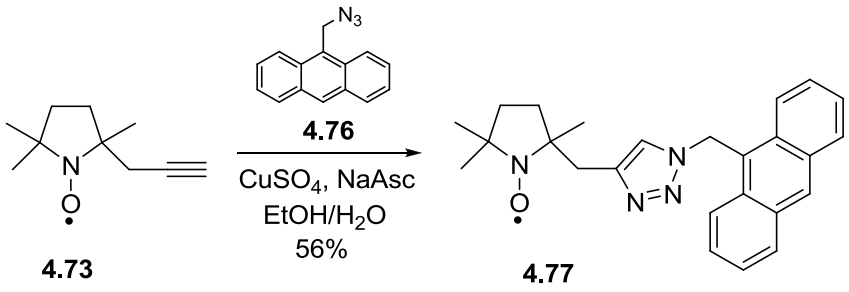
TLC: 3:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.57.

IR ($CDCl_3$): 3294, 2972, 2118, 1459, 1368 cm^{-1}.

Melting point: 36-38 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$, addition of phenylhydrazine): δ 2.43 and 2.35 (AB spin system, d, *J* = 16 Hz, 2H), 1.98 (s, 1H), 1.90 (m, 1H), 1.73 (m, 1H), 1.65 (t, *J* = 7 Hz, 2H), 1.32 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$, addition of phenylhydrazine): δ 82.9 (C), 69.0 (CH), 65.2 (C), 63.8 (C), 34.4 (CH_2), 32.8 (CH_2), 31.1 (CH_2), 27.5 (CH_3), 23.2 (CH_3), 22.7 (CH_3) ppm.



2-((1-(Anthracen-9-ylmethyl)-*1H*-1,2,3-triazol-4-yl)methyl)-2,5,5-trimethylpyrro lidin-*N*-oxyl (4.77). Following the general procedure of Fairfull-Smith *et al*.,[17] to a solution of 2,2,5-trimethyl-5-(prop-2-ynyl)pyrrolidin-*N*-oxyl (**4.73**, 120 mg, 0.72 mmol) and 9-(azidomethyl)anthracene (**4.76**, 177 mg, 0.759 mmol) in 1:1 ethanol/water (22 mL) was added copper sulfate (6 mg, 0.04 mmol) and sodium ascorbate (29 mg, 0.15 mmol). The reaction mixture was stirred vigorously in the dark overnight at room temperature. The next day, the mixture was concentrated *in vacuo* to give 230 mg of a green oil. The oil was purified by silica gel column chromatography with 4:1 hexanes/ethyl acetate, followed by 1:1 hexanes/ethyl

acetate, and finally with 1:2 hexanes/ethyl acetate to give 160 mg (56% yield) of the title compound as an orange oil.

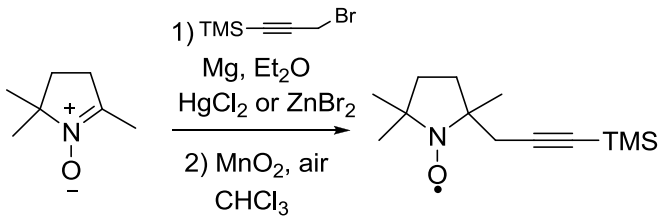
TLC: 1:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.31.

IR ($CDCl_3$): 2971, 2238, 1444, 1047, 911, 728 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$, addition of phenylhydrazine): δ 8.51 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 2H), 8.02 (d, *J* = 7.8 Hz, 2H), 7.49 (m, 4H), 6.85 (s, 1H), 6.41 and 6.36 (AB spin system, d, *J* = 15 Hz, 2H), 2.56 (s, 2H), 1.52 (m, 1H), 1.44 (m, 1H), 1.25 (m, 1H), 1.05 (s, 3H), 0.96 (s, 3H), 0.73 (m, 1H), 0.58 (s, 3H) ppm.

^{13}C NMR, DEPT (150 MHz, $CDCl_3$, addition of phenylhydrazine): δ 145.5 (C), 131.4 (C), 130.7 (C), 129.6 (CH), 129.4 (CH), 128.3 (C), 127.5 (CH), 125.4 (CH), 124.1 (C), 123.0 (CH), 122.1 (CH), 64.7 (C), 63.0 (C), 42.6 (CH_2), 37.6 (CH_2), 34.4 (CH_2), 32.3 (CH_2), 28.0 (CH_3), 23.6 (CH_3), 21.9 (CH_3) ppm.

HRMS: M+1 ($C_{25}H_{29}N_4O^+$, addition of phenylhydrazine) 401.2336 calcd; 401.2342 obsd.



4.44 **4.78** 64% ($HgCl_2$) 56% ($ZnBr_2$)

2,2,5-Trimethyl-5-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-*N*-oxyl (4.78). Following the general procedure of Kobayashi *et al*.,[18] mercuric chloride (43 mg, 0.16 mmol) or zinc bromide (36 mg, 0.16 mmol) and magnesium turnings (235 mg, 7.98 mmol (for $HgCl_2$), 382 mg, 15.7 mmol (for $ZnBr_2$)) were vigorously stirred in diethyl ether (9 mL) at room temperature for one hour. The solution turned grey, and bromo-1-trimethylsilyl-1-propyne (1.20 mL, 8.31 mmol) was added. The reaction mixture was allowed to stir for the next two hours. The resulting Grignard solution was then added slowly to a solution of 3,4-dihydro-2,2,5-trimethyl-2H-pyrrole-1-oxide (**4.44**, 500 mg, 4 mmol) in diethyl ether (4 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for two hours. The reaction was cooled to 0 °C, and then quenched with saturated ammonium chloride (10 mL). The reaction mixture was taken up with diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with brine (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give an orange oil. The oil was dissolved in chloroform (13 mL), and manganese dioxide (171 mg, 1.97 mmol) was added. Air was bubbled through the solution for 30 minutes. The mixture

was filtered through a celite pad, and rinsed with chloroform. The filtrate was concentrated *in vacuo* to give an orange oil. The oil was purified by silica gel column chromatography with 4:1 hexanes/ethyl acetate to give 598 mg (64% yield, for $HgCl_2$) or 527 mg (56% yield, for $ZnBr_2$) of the title compound as an orange oil.

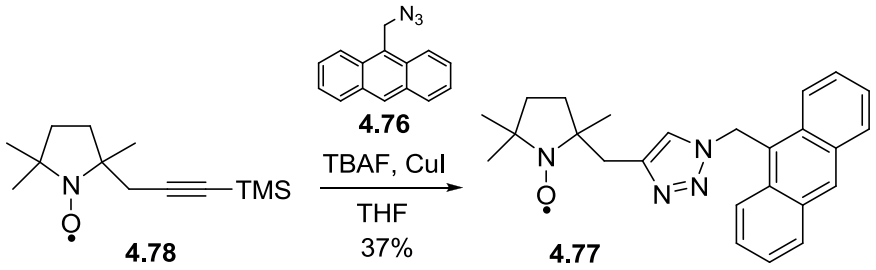
TLC: 4:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.62.

IR ($CDCl_3$): 2969, 2176, 1459, 1367, 1250, 843 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, addition of phenylhydrazine): δ 2.44 and 2.40 (AB spin system, d, *J* = 16.5 Hz, 2H), 1.91 (m, 1H), 1.74 (m, 1H), 1.65 (t, *J* = 6.5 Hz, 2H), 1.31 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 0.17 (s, 9H) ppm.

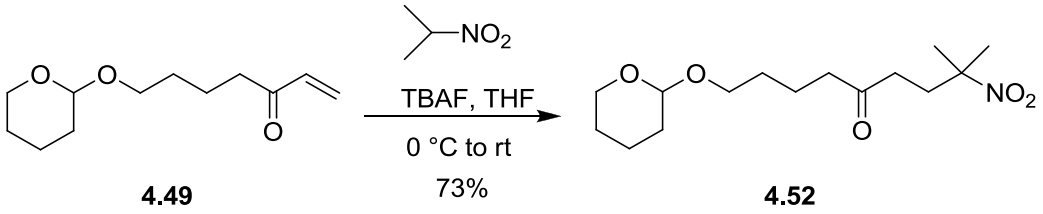
^{13}C NMR, DEPT (125 MHz, $CDCl_3$, addition of phenylhydrazine): δ 106.1 (C), 85.7 (C), 66.1 (C), 64.5 (C), 34.7 (CH_2), 33.1 (CH_2), 32.7 (CH_2), 27.6 (CH_3), 23.2 (CH_3), 23.1 (CH_3), 0.15 (CH_3) ppm.

HRMS: M+1 ($C_{13}H_{26}NOSi^+$, addition of phenylhydrazine) 240.1778 calcd; 240.1786 obsd.



2-((1-(Anthracen-9-ylmethyl)-*1H*-1,2,3-triazol-4-yl)methyl)-2,5,5-trimethylpyrro lidin-*N*-oxyl (4.77). To a solution of 2,2,5-trimethyl-5-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-*N*-oxyl (**4.78**, 106 mg, 0.444 mmol), 9-(azidomethyl)anthracene (**4.76**, 109 mg, 0.467 mmol) and copper (I) iodide (9 mg, 0.05 mmol) in tetrahydrofuran (9 mL) was added tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.53 mL, 0.53 mmol) at room temperature. The reaction mixture was allowed to stir in the dark overnight. The next day, the mixture was concentrated *in vacuo* to give 145 mg of an orange oil. The oil was purified by silica gel column chromatography with 1:1 hexanes/ethyl acetate, followed by 1:2 hexanes/ethyl acetate to give 66 mg (37% yield) of the title compound as an orange oil.

^{1}H-NMR spectrum was identical to **4.77** prepared by click reaction of alkynyl nitroxide **4.73** using copper sulfate and sodium ascorbate.



4.49 **4.52**

8-Methyl-8-nitro-1-(tetrahydro-2*H*-pyran-2-yloxy)nonan-5-one (4.52). To a solution of 2-nitropropane (3.50 mL, 37.8 mmol) and 7-(tetrahydro-2*H*-pyran-2-yloxy) hept-1-en-3-one (**4.49**, 7.395 g, 34.83 mmol) in tetrahydrofuran (116 mL) was added tetrabutylammonium fluoride (TBAF, 1 M in THF, 17.40 mL, 17.40 mmol) at 0 °C. The mixture was allowed to warm to room temperature overnight. To quench the reaction, saturated ammonium chloride (120 mL) was added. The aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 10.987 g of a brown oil. The oil was purified by silica gel column chromatography with 2:1 hexanes/ethyl acetate to give 7.663 g (73% yield) of the title compound as a colorless oil.

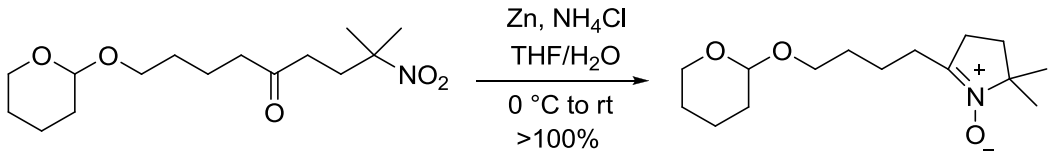
TLC: 2:1 hexane:ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.50.

IR ($CDCl_3$): 2923, 2869, 1717, 1538, 1033 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 4.54 (t, *J* = 3.5 Hz, 1H), 3.83 (m, 1H), 3.72 (m, 1H), 3.47 (m, 1H), 3.36 (m, 1H), 2.44 (t, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 1.81-1.48 (m, 10H), 1.56 (s, 6H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$): δ 208.8 (C), 99.1 (CH), 87.6 (C), 67.3 (CH_2), 62.6 (CH_2), 42.8 (CH_2), 37.4 (CH_2), 34.2 (CH_2), 30.9 (CH_2), 29.3 (CH_2), 26.1 (CH_3), 25.6 (CH_2), 20.8 (CH_2), 19.8 (CH_2) ppm.

HRMS: M+1 ($C_{15}H_{28}NO_5^+$) 302.1962 calcd; 302.1968 obsd.



4.52 **4.53**

2,2-Dimethyl-5-(4-(tetrahydro-2*H*-pyran-2-yloxy) butyl)-3,4-dihydro-2*H*-pyrrole-1-oxide (4.53). To a solution of 8-methyl-8-nitro-1-(tetrahydro-2*H*-pyran-2-yloxy) nonan-5-one (**4.52**) (8.764 g, 29.08 mmol) and ammonium chloride (1.711 g, 31.99 mmol) in tetrahydrofuran (140 mL) and water (140 mL) was added zinc powder (7.606 g, 116.3 mmol) at 0 °C over 15 minutes. The reaction mixture was allowed to warm to room temperature open to the atmosphere overnight. The mixture was filtered through a celite pad, and rinsed with chloroform. The aqueous layer was extracted with chloroform (3 × 50 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 8.0292 g (>100% yield) of the title compound as a yellowish oil. The crude compound was used in the next step without purification.

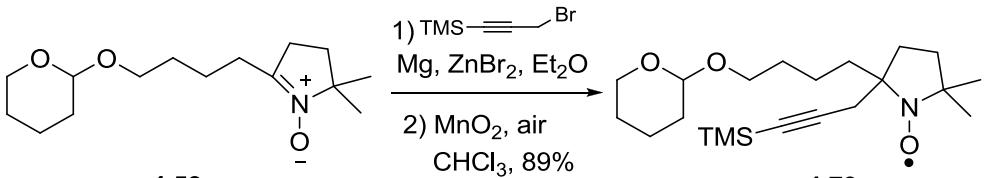
IR ($CDCl_3$): 2941, 2869, 1457, 1365, 1137, 1033 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56 (t, *J* = 2.5 Hz, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 3.49 (m, 1H), 3.41 (m, 1H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.97 (t, *J* = 7.5 Hz, 2H), 1.82-1.49 (m, 10H), 1.39 (s, 6H).

^{1}H NMR (500 MHz, C_6D_6): δ 4.55 (t, *J* = 3.5 Hz, 1H), 3.83-3.77 (m, 2H), 3.41-3.30 (m, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 1.94 (t, *J* = 7.5 Hz, 2H), 1.76-1.24 (m, 10H), 1.36 (t, *J* = 7.5 Hz, 2H), 1.23 (s, 6H) ppm.

^{13}C NMR, DEPT (125 MHz, C_6D_6): δ 140.9 (C), 99.1 (CH), 73.1 (C), 67.4 (CH_2), 62.2 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 30.3 (CH_2), 27.3 (CH_2), 27.1 (CH_2), 26.3 (CH_2), 25.9 (CH_3), 22.7 (CH_2), 20.2 (CH_2) ppm.

HRMS: M+1 ($C_{15}H_{28}NO_3^+$) 270.2064 calcd; 270.2070 obsd.



4.53 **4.79**

2,2-Dimethyl-5-(4-(tetrahydro-*2H*-pyran-2-yloxy)butyl)-5-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-*N*-oxyl (4.79). Following the general procedure of Kobayashi *et al*.,[18] magnesium turnings (2.527 g, 103.9 mmol) and zinc bromide (117 mg, 0.509 mmol) were vigorously stirred in diethyl ether (65 mL) at room temperature for 30 minutes. The solution turned grey, and bromo-1-trimethylsilyl-1-propyne (7.50 mL, 51.9 mmol) was added. The reaction mixture was allowed to stir at 0 ^{o}C for two hours.

The resulting Grignard solution was then added slowly to a solution of 2,2-dimethyl-5-(4-(tetrahydro-2*H*-pyran-2-yloxy)butyl)-3,4-dihydro-2*H*-pyrrole-1-oxide (**4.53**, 7.834 g, 25.99 mmol) in diethyl ether (22 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1.5 hours. The reaction was cooled to 0 °C, and then quenched with saturated ammonium chloride (50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give an orange oil. The oil was dissolved in chloroform (87 mL), and manganese dioxide (1.130 g, 12.99 mmol) was added. Air was bubbled through the solution for one hour. The mixture was filtered through a celite pad, and rinsed with chloroform. The filtrate was concentrated *in vacuo* to give 9.956 g of an orange oil. The oil was purified by silica gel column chromatography with 3:1 hexanes/ethyl acetate to give 8.828 g (89% yield) of the title compound as an orange oil.

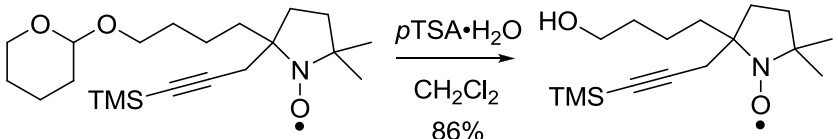
TLC: 3:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.45.

IR ($CDCl_3$): 2944, 2176, 1462, 1249, 1034, 843 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$, addition of phenylhydrazine, two diastereomers): δ 4.61 (m, 1H), 3.91 (m, 1H), 3.79 (m, 1H), 3.54 (m, 1H), 3.45 (m, 1H), 2.55 and 2.45 (AB spin system, dd, *J* = 3.6, 16.8 Hz, 2H), 1.87-1.41 (m, 16H), 1.18 (s, 3H), 1.16 (s, 3H), 0.18 (s, 9H) ppm.

^{13}C NMR, DEPT (150 MHz, $CDCl_3$, addition of phenylhydrazine, two diastereomers): δ 106.4 (C), 99.1 (CH), 98.9(CH), 85.8 (C), 67.7 (C), 67.5 (C), 62.6 (C), 62.5 (C), 37.6(CH_2), 37.3 (CH_2), 34.8 (CH_2), 31.3 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 25.6 (CH_2), 24.4 (CH_3), 24.3 (CH_3), 21.3 (CH_2), 21.0 (CH_2), 19.9 (CH_2), 19.8 (CH_2) ppm.

HRMS: M+1 ($C_{21}H_{40}NO_3Si^+$, addition of phenylhydrazine) 382.2772 calcd; 382.2782 obsd.



4.79 **4.80**

2-(4-Hydroxybutyl)-5,5-dimethyl-2-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-*N*-oxyl (4.80). To a solution of 2,2-dimethyl-5-(4-(tetrahydro-*2H*-pyran-2-yloxy)butyl)-5-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-*N*-oxyl (**4.79**, 2.719 g, 7.143 mmol) in tetrahydrofuran (122 mL) and MeOH (61 mL) was added *p*-toluenesulfonic acid monohydrate (137 mg, 0.714 mmol). The reaction mixture was allowed to stir at room temperature overnight. Saturated sodium bicarbonate (100 mL) was added. The aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 2.056 g of an orange oil. The oil was purified by silica

gel column chromatography with 1:1 hexanes/ethyl acetate to give 1.819 g (86% yield) of the title compound as an orange oil.

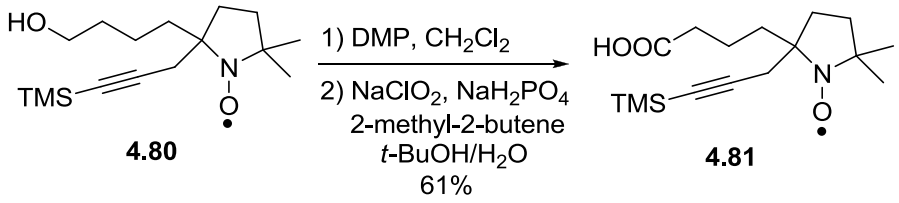
TLC: 1:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.29.

IR ($CDCl_3$): 3419 (br), 2975, 2868, 1445, 1367, 1216, 760, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$, addition of phenylhydrazine): δ 3.76 (br m, 2H), 2.58 and 2.46 (AB spin system, d, J = 16.8 Hz, 2H), 1.92-1.50 (br m, 10H), 1.18 (s, 6H), 0.18 (s, 9H) ppm.

^{13}C NMR, DEPT (150 MHz, $CDCl_3$, addition of phenylhydrazine): δ 106.1 (C), 85.9 (C), 67.9 (C), 64.6 (C), 62.4 (CH_2), 37.3 (CH_2), 34.8 (CH_2), 33.1 (CH_2), 31.5 (CH_2), 28.5 (CH_2), 26.2 (CH_3), 24.0 (CH_3), 20.4 (CH_2), 0.17 (CH_3) ppm.

HRMS: M+1 ($C_{16}H_{32}NO_2Si^+$) 298.2197 calcd; 298.2203 obsd.



4.80 **4.81**

4-(*N*-Oxyl-5,5-dimethyl-2-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-2-yl)butanoic acid (4.81). To a solution of 2-(4-hydroxybutyl)-5,5-dimethyl-2-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-*N*-oxyl (**4.80**, 1.061 g, 3.577 mmol) in dichloromethane (28 mL) was added Dess-Martin periodinane[2] (2.276 g, 5.366 mmol) at 0 °C. The reaction mixture was allowed to stir for four hours. The mixture

was filtered through a celite pad, and rinsed with dichloromethane. The filtrate was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 1.028 g of an orange oil. Following the general procedure of Weerasooriya *et al*.,[19] the resulting oil was suspended in *tert*-butanol (22 mL) and water (4.50 mL). Sodium phosphate (1.288 g, 10.73 mmol) and 2-methyl-2-butene (2.30 mL, 21.6 mmol) were added. The mixture was cooled in an ice bath before a solution of sodium chlorite (2.426 g, 21.46 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature overnight open to the atmosphere. The next day, 1 M sulfuric acid was added dropwise to adjust the pH to 1. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 1.235 g of an orange oil. The oil was purified by silica gel column chromatography with 2:1 hexanes/ethyl acetate to give 679 mg (61% yield) of the title compound as an orange solid.

TLC: 2:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.33.

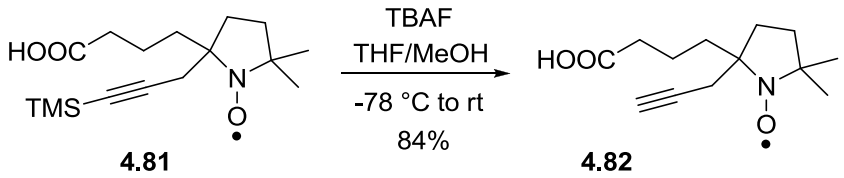
Melting point: 107-109 ^{o}C.

IR ($CDCl_3$): 2960, 2177, 1705, 1408, 1249, 840 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6, addition of phenylhydrazine): δ 2.84 and 2.58 (AB spin system, d, J = 17.5 Hz, 2H), 2.50-1.39 (br m, 10H), 1.26 (s, 3H), 0.99 (s, 3H), 0.26 (s, 9H) ppm.

^{13}C NMR, DEPT (125 MHz, C_6D_6, addition of phenylhydrazine): δ 179.5 (C), 103.2 (C), 73.0 (C), 87.6 (C), 73.1 (C), 69.5 (C), 37.5 (CH_2), 35.6 (CH_2), 33.9 (CH_2), 31.6 (CH_2), 25.8 (CH_2), 24.6 (CH_3), 21.8 (CH_3), 20.5 (CH_2), 0.05 (CH_3).

HRMS: M+Na$^+$ ($C_{16}H_{29}NNaO_3Si^+$, addition of phenylhydrazine) 334.1809 calcd; 334.1819 obsd.



4.81 **4.82**

4-(*N*-Oxyl-5,5-dimethyl-2-(prop-2-ynyl)pyrrolidin-2-yl)butanoic acid (4.82). To a solution of 4-(*N*-oxyl-5,5-dimethyl-2-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-2-yl)butanoic acid (**4.81**, 351 mg, 1.13 mmol) in tetrahydrofuran (9 mL) and MeOH (0.45 mL) was added tetrabutylammonium fluoride (TBAF, 1 M in THF, 1.10 mL, 1.10 mmol) at -78 °C. The reaction mixture was allowed to warm to room temperature overnight. Saturated ammonium chloride (10 mL) was added. 1 M Sulfuric acid was added dropwise to adjust the pH to 1. The aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 467 mg of a brown oil. The oil was purified by silica gel column chromatography with 1:1 hexanes/ethyl

acetate, followed by 1:2 hexanes/ethyl acetate to give 226 mg (84% yield) of the title compound as an orange oil.

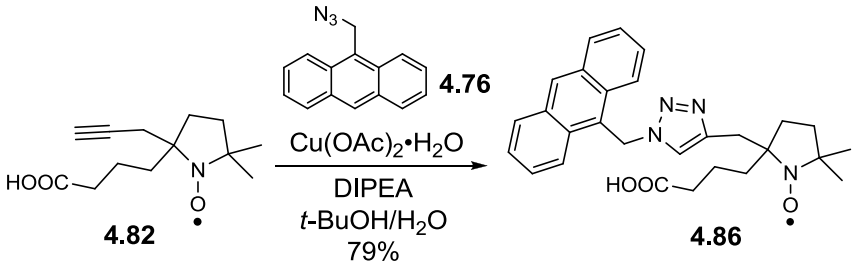
TLC: 1:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.40.

IR ($CDCl_3$): 3287 (br), 2972, 2118, 1709, 1461, 1181 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, addition of phenylhydrazine): δ 2.81 and 2.60 (AB spin system, d, *J* = 14.5 Hz, 2H), 2.39-2.22 (m, 2H), 2.03 (s, 1H), 1.94-1.15 (m, 8H), 1.36 (s, 3H), 1.30 (s, 3H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$, addition of phenylhydrazine): δ 78.7 (C), 73.4 (C), 71.4 (CH), 70.5 (C), 37.3 (CH_2), 35.9 (CH_2), 34.3 (CH_2), 32.0 (CH_2), 24.8 (CH_3), 24.2 (CH_2), 22.1 (CH_3), 20.4 (CH_2) ppm.

HRMS: $M+Na^+$ ($C_{13}H_{21}NNaO_3^+$) 262.1414 calcd; 262.1416 obsd.



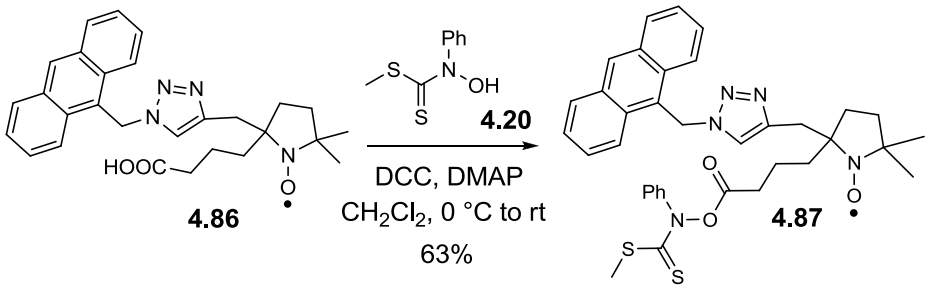
4-(2-((1-(Anthracen-9-ylmethyl)-*1H*-1,2,3-triazol-4-yl)methyl)-*N*-oxyl-5,5-dimethyl pyrrolidin-2-yl)butanoic acid (4.86). Following the general procedure of Zhu *et al*.,[20] to a solution of 4-(*N*-oxyl-5,5-dimethyl-2-(prop-2-ynyl)pyrrolidin-2-yl)butanoic acid (**4.82**, 72 mg, 0.30 mmol), 9-(azidomethyl)anthracene (**4.76**, 70 mg, 0.30 mmol) and

diisopropylethylenediamine (DIPEA, 54 μL, 0.30 mmol) in *tert*-butanol (4 mL) was added copper acetate monohydrate (6 mg, 0.03 mmol) in water (4 mL) at room temperature. The reaction mixture was allowed to stir in the dark overnight. The next day, the mixture was taken up with dichloromethane (10 mL). 1 M Sulfuric acid was added to the aqueous layer until achieving a pH~1. The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was concentrated *in vacuo* to give 140 mg of a green oil. The oil was purified by silica gel column chromatography with 1:2 hexanes/ethyl acetate, followed by 100% ethyl acetate, and finally with 100% methanol to give 112 mg (79% yield) of the title compound as a yellowish oil.

NMR spectra could not be obtained, presumably due to coordination of the compound to copper ion.

IR ($CDCl_3$): 3412 (br), 2970, 1563, 1447, 729 cm^{-1}.

LRMS: M+1 ($C_{28}H_{32}N_4O_3$) 472.2, M+Na^+ ($C_{28}H_{31}N_4NaO_3^+$) 494.2, M+K^+ ($C_{28}H_{32}N_4KO_3^+$) 510.2



Methyl 4-(2-((1-(anthracen-9-ylmethyl)-*1H*-1,2,3-triazol-4-yl)methyl)-*N*-oxyl-5,5-dimethylpyrrolidin-2-yl)butanoyloxy(phenyl)carbamodithioate (4.87). Following the general procedure of Renaud *et al*.,[12] to a solution of 4-(2-((1-(anthracen-9-ylmethyl)-*1H*-1,2,3-triazol-4-yl)methyl)-*N*-oxyl-5,5-dimethyl pyrrolidin-2-yl)butanoic acid (**4.86**, 15 mg, 0.032 mmol) in dichloromethane (2 mL) was added 1,3-dicyclohexylcarbodiimide (DCC, 7 mg, 0.03 mmol) and 4-dimethylaminopyridine (DMAP, 1 mg, 0.008 mmol) at 0 °C, and the reaction mixture was stirred for one hour. The flask was covered with aluminum foil, and methyl hydroxyl (phenyl)carbamodithioate (**4.20**, 7 mg, 0.04 mmol) was added at 0 °C. The mixture was allowed to warm to room temperature overnight. The next day, the reaction mixture was concentrated *in vacuo* to give 25 mg of a yellowish oil. The oil was purified by silica gel column chromatography with 1:1 hexanes/ethyl acetate to give 15 mg (63% yield) of the title product as a fluffy light yellowish solid. Note: the title product could not be isolated from by-product dicyclohexylurea.

TLC: 1:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.31.

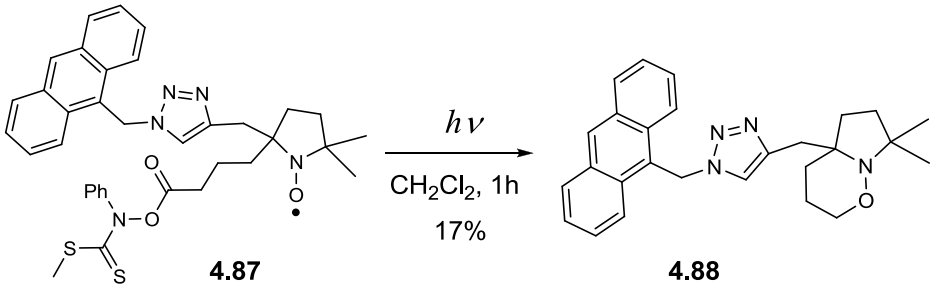
Melting point: 72-75 ^{o}C.

IR: ($CDCl_3$) 3323, 2927, 1795, 1624, 1359, 1047, 729 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$, addition of phenylhydrazine): δ 8.57 (s, 1H), 8.26 (d, *J* = 9.0 Hz, 2H), 8.06 (d, *J* = 9.0 Hz, 2H), 7.58 (dt, *J* = 1.2, 7.8 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 6.84 (s, 1H), 6.48 (s, 2H), 3.09 (dt, *J* = 4.2, 12.0 Hz, 2H), 2.86 and 2.62 (AB spin system, d, *J* = 15 Hz, 2H), 2.59 (s, 3H), 2.35 (1H), 2.11 (1H), 1.72-1.52 (m, 4H), 1.34-1.21 (m, 3H), 1.12 (s, 3H), 1.09 (s, 3H) ppm.

^{13}C NMR, DEPT (125 MHz, $CDCl_3$, addition of phenylhydrazine): δ 199.1 (C), 179.2 (C), 157.0 (C), 144.3 (C), 131.6 (C), 131.0 (C), 130.0 (CH), 129.7 (CH), 129.6 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 125.6 (CH), 124.0 (C), 123.0 (CH), 123.1 (CH), 121.8 (CH), 66.0 (C), 64.2 (C), 46.5 (CH_2), 38.7 (CH_2), 34.4 (CH_2), 39.9 (CH_2), 33.5 (CH_2), 28.8 (CH_2), 28.5 (CH_3), 21.0 (CH_3), 19.5 (CH_3), 19.2 (CH_2) ppm.

HRMS: M+1 ($C_{36}H_{40}N_5O_3S_2^+$, addition of phenylhydrazine) 654.2567 calcd; 654.2575 obsd.



4-((1-(Anthracen-9-ylmethyl)-*1H*-1,2,3-triazol-4-yl)methyl)-7,7-dimethylhexahydro-*2H*-pyrrolo[1,2]oxazine (4.88). Following a modified procedure of Renaud *et al.*,[12] a

solution of methyl 4-(2-((1-(anthracen-9-ylmethyl)-*1H*-1,2,3-triazol-4-yl)methyl)-*N*-oxyl-5,5-dimethylpyrrolidin-2-yl)butanoyloxy(phenyl)carbamodithioate (**4.87**, 19 mg, 0.029 mmol) in degassed dichloromethane (3 mL) was irradiated with a 200 W high pressure mercury lamp under nitrogen for an hour. The reaction mixture was concentrated *in vacuo* to give 18 mg of an orange oil. The oil was purified by silica gel column chromatography with 2:1 hexanes/ethyl acetate to give 2 mg (17% yield) of the title product as a yellowish oil. Note: the title product could not be isolated from by-product dicyclohexylurea.

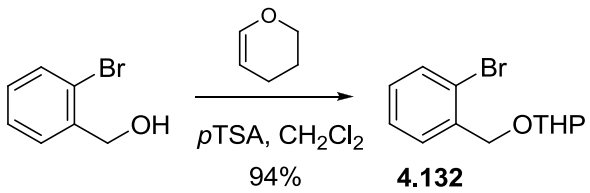
TLC: 2:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.50.

IR: ($CDCl_3$) 2932, 2852, 1673, 1449, 1261, 1050, 910, 800, 730 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.30 (d, *J* = 9.0 Hz, 2H), 8.08 (d, *J* = 9.0 Hz, 2H), 7.59 (dt, *J* = 1.5, 7.0 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 2H), 6.88 (s, 1H), 6.54 and 6.50 (AB spin system, *J* = 15 Hz, 2H), 3.78 (m, 2H), 3.09 and 2.67 (AB spin system, *J* = 14 Hz, 2H), 1.74-1.12 (m, 8H), 1.10 (s, 3H), 0.87 (s, 3H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 145.8 (C), 131.6 (C), 131.0 (C), 129.9 (CH), 129.6 (CH), 127.7 (CH), 125.5 (CH), 124.2 (C), 123.2 (CH), 121.6 (CH), 69.5 (CH_2), 63.9 (C), 60.8 (C), 46.4 (CH_2), 35.3 (CH_2), 32.9 (CH_2), 32.4 (CH_2), 29.3 (CH_3), 27.8 (CH_2), 26.1 (CH_3), 20.9 (CH_2) ppm.

HRMS: M+1 ($C_{27}H_{31}N_4O^+$) 427.2492 calcd; 427.2498 obsd.

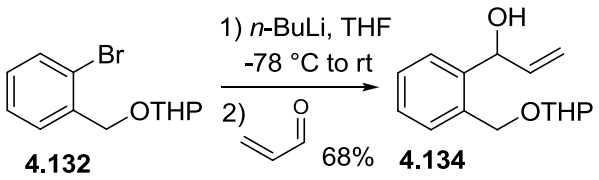


2-(2-Bromobenzyloxy)tetrahydro-*2H*-pyran (4.132).[21] To a solution of 2-bromobenzyl alcohol (20.003 g, 106.97 mmol) and 3,4-dihydro-2*H*-pyran (10.80 mL, 116.9 mmol) in dichloromethane (214 mL) was added *p*-toluenesulfonic acid monohydrate (205 mg, 1.07 mmol). The reaction mixture was allowed to stir at room temperature overnight. The mixture was quenched with saturated sodium bicarbonate (100 mL). The aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 28.905 g of a brownish oil. The oil was purified by silica gel column chromatography with 3:1 hexanes/ethyl acetate to give 26.709 g (94% yield) of the title compound as a colorless oil.

TLC: 4:1 hexanes:ethyl acetate, *p*-anisaldehyde stain, R_f = 0.62.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 4.83 (d, *J* = 13.2 Hz, 1H), 4.79 (t, *J* = 3.0 Hz, 1H), 4.57 (d, *J* = 13.2 Hz, 1H), 3.94 (dt, *J* = 3.0, 11.4 Hz, 1H), 3.58 (m, 1H), 1.93-1.56 (m, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 137.7, 132.5, 129.0, 128.8, 127.4, 122.7, 98.4, 68.6, 62.2, 30.5, 25.5, 19.4 ppm.



4.132 **4.134**

1-(2-((Tetrahydro-*2H*-pyran-2-yloxy)methyl)phenyl)prop-2-en-1-ol (4.134). To a solution of 2-(2-bromobenzyloxy)tetrahydro-*2H*-pyran (**4.132**, 11.738 g, 43.290 mmol) in degassed tetrahydrofuran (144 mL) chilled at -78 °C was added slowly *n*-butyl lithium (1.6 M in hexanes, 40.6 mL, 65.0 mmol). The solution was stirred at this temperature for 30 minutes. Acrolein (4.35 mL, 65.2 mmol) was added at -78 °C, and the reaction was allowed to warm to room temperature overnight. The next day, saturated ammonium chloride (75 mL) was added at 0 °C to quench the reaction. The aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 15.002 g of an orange oil. The oil was purified by silica gel column chromatography with 4:1 hexanes/ethyl acetate to give 7.509 g (68% yield) of the title compound as a yellowish oil.

TLC: 5:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.19.

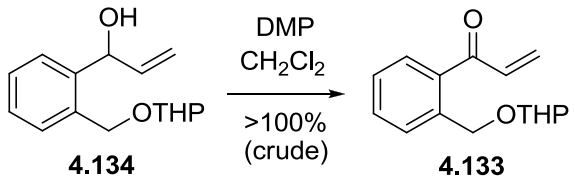
IR: ($CDCl_3$) 3414 (br), 2943, 1118, 1023, 759 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.48-7.28 (m, 8H), 6.15 (m, 2H), 5.51 (m, 2H), 5.46 (dd, *J* = 1.5, 17.5 Hz, 2H), 5.29 (dd, *J* = 1.5, 10.5 Hz, 2H), 4.96 and 4.89 (AB spin system, d, *J* = 11.5 Hz, 2H), 4.75 (t, *J* = 3.0 Hz, 2H), 4.68 and 4.60 (AB

spin system, d, *J* = 11.5 Hz, 2H), 3.89 (m, 2H), 3.57 (m, 2H), 3.19 (br s, 2H), 1.87-1.54 (m, 12H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$, two diastereomers): δ 142.1 (C), 139.3 (CH), 135.5(C), 130.5 (CH), 130.4 (CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 115.0 (CH_2), 98.1 (CH), 97.8 (CH), 71.8 (CH), 67.7 (CH_2), 67.5 (CH_2), 62.3 (CH_2), 62.2 (CH_2), 30.5 (CH_2), 25.4 (CH_2), 19.2 (CH_2) ppm.

HRMS: M+1 ($C_{15}H_{21}O_3^+$) 249.1485 calcd; 249.1493 obsd.



4.134 **4.133**

1-(2-((Tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)prop-2-en-1-one (4.133). To a solution of 1-(2-((tetrahydro-*2H*-pyran-2-yloxy)methyl)phenyl)prop-2-en-1-ol (**4.134**, 7.500 g, 30.20 mmol) in dichloromethane (300 mL) was added Dess-Martin periodinane[2] (16.653 g, 39.263 mmol) and hydroquinone (166 mg, 1.51 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The next day, the mixture was filtered through a celite pad, and rinsed with dichloromethane. The filtrate was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 7.924 g of an orange oil. Trace of Dess-Martin periodinane by-product was removed

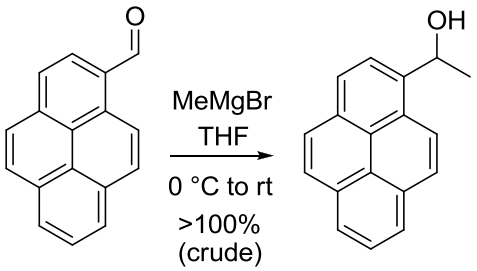
by silica gel plug using 2:1 hexanes/ethyl acetate as eluent to give 7.709 g of the title compound as a yellowish oil (>100% crude yield) was stored in the presence of hydroquinone to prevent polymerization.

IR: ($CDCl_3$) 2942, 1667, 1401, 1023, 757 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 0.5, 7.5 Hz, 1H), 7.49 (m, 2H), 7.36 (dd, *J* = 1.0, 7.5 Hz, 1H), 6.80 (dd, *J* = 10.5, 17.5 Hz, 2H), 6.16 (dd, *J* = 1.5, 17.5 Hz, 1H), 6.01 (dd, *J* = 1.5, 10.5 Hz, 2H), 4.94 and 4.70 (AB spin system, d, *J* = 13.5 Hz, 2H), 4.67 (t, *J* = 3.5 Hz, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 1.86-1.49 (6H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 196.0 (C), 138.4 (C), 136.9 (C), 136.2 (CH), 131.3 (CH_2), 131.1 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 98.5 (CH), 67.0 (CH_2), 62.2 (CH_2), 30.4 (CH_2), 25.4 (CH_2), 19.3 (CH_2) ppm.

HRMS: M+1 ($C_{15}H_{19}O_3^+$) 247.1329 calcd; 247.1341 obsd.



4.135 **4.136**

1-(Pyren-1-yl)ethanol (4.136). To a solution 1-pyrenecarboxaldehyde (12.020 g, 51.678 mmol) in tetrahydrofuran (172 mL) was added methylmagnesium bromide (1.0 M in THF, 77.5 mL, 77.5 mmol) at 0 °C. The reaction was allowed to warm to

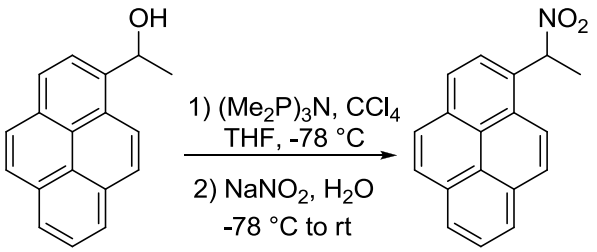
room temperature overnight. The next day, saturated ammonium chloride (150 mL) was added at 0 °C to quench the reaction. The aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 12.926 g (>100% crude yield) of the title product as an orange solid. The product was used in the next step without purification.

IR: ($CDCl_3$) 3367 (br), 3041, 2970, 1084, 1068, 843 cm^{-1}.

Melting point: 108-110 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.32-8.00 (m, 9H), 5.95 (q, *J* = 6.0 Hz, 1H), 2.21 (br s, 1*J* = 6.0 Hz, 3H) ppm.^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 139.2 (C), 131.5 (C), 130.8 (C), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.0 (CH), 125.4 (CH), 125.2 (CH), 125.1 (CH), 122.6 (CH), 122.5 (CH), 67.4 (CH), 25.1 (CH_3) ppm.

HRMS: M+1 ($C_{18}H_{15}O^+$) 247.1117 calcd; 247.1125 obsd.



4.136 **4.138**

1-(1-Nitroethyl)pyrene (4.138). Following the general procedure of Castro and Selve,[22] to a vigorously stirring solution of 1-(pyren-1-yl)ethanol (**4.136**, 7.676 g, 31.16 mmol) and carbon tetrachloride (8.30 mL, 85.6 mL) in tetrahydrofuran (78 mL) was slowly added hexamethylphosphorus triamide (6.00 mL, 32.0 mmol) at -78 °C. During the addition, the temperature was maintained below -60 °C. A solution of sodium nitrite (4.300 g, 62.32 mmol) in water (21 mL) was then added. A yellow precipitate was formed during the addition, and the solution turned from orange to green in color. The reaction mixture was allowed to stir at room temperature overnight. The next day, the aqueous layer was extracted with diethyl ether (2 $\times$ 100 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 5.856 g of the title product as a brown oil. The oil was purified by silica gel column chromatography with 3:1 hexanes/ethyl acetate to give 3.744 g (44% yield) of the title compound as a yellowish solid.

TLC: 2:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.53.

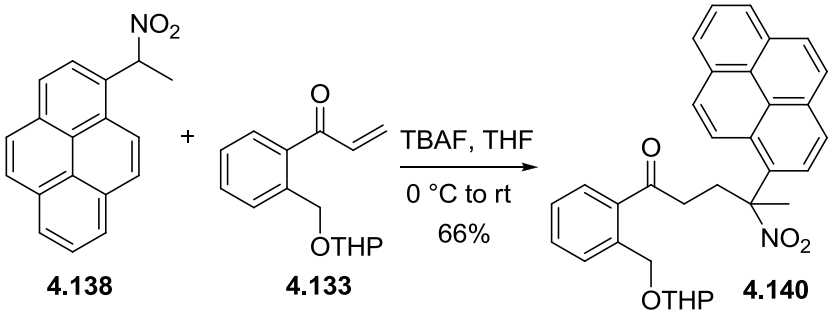
Melting point: 150-151 °C.

IR: ($CDCl_3$) 3584 (br), 3043, 1546, 1384, 1350, 845 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.35-8.02 (m, 9H), 6.77 (q, *J* = 5.5 Hz, 1H), 2.21 (d, *J* = 5.5 Hz, 3H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 132.2 (C), 131.2 (C), 130.4 (C), 129.2 (CH), 129.0 (C), 128.5 (CH), 128.2 (C), 127.2 (CH), 126.3 (CH), 126.1 (CH), 125.8 (CH), 125.1 (CH), 124.8 (C), 124.5 (C), 123.9 (CH), 121.3 (CH), 82.2 (CH), 19.9 (CH_3) ppm.

HRMS: M+1 ($C_{18}H_{14}NO_2^+$) 276.1019 calcd; 276.1031 obsd.



4.138 **4.133** **4.140**

4-(3,6-Dihydropyren-1-yl)-4-nitro-1-(2-((tetrahydro-2H-pyran-2-yloxy)methyl) phenyl)pentan-1-one (4.140). To a solution of 1-(1-nitroethyl)pyrene (**4.138**, 3.285 g, 11.93 mmol) and 1-(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)prop-2-en-1-one (**4.133**, 2.938 g, 11.93 mmol) in tetrahydrofuran (40 mL) was added tetrabutylammonium fluoride (TBAF, 1 M in THF, 6.00 mL, 6.00 mmol) at 0 °C. The mixture was allowed to warm to room temperature overnight. To quench the

reaction, saturated ammonium chloride (50 mL) was added. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 6.554 g of a brown oil. The oil was purified by silica gel column chromatography with 2:1 hexanes/ethyl acetate to give 3.883 g (66% yield) of the title compound as a fluffy yellowish solid.

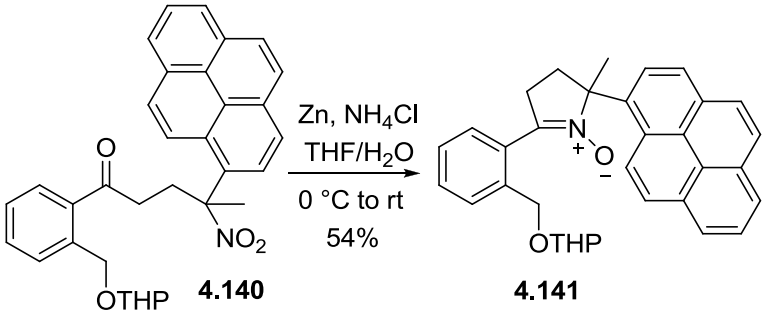
TLC: 2:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.35.

IR: ($CDCl_3$) 2943, 1681, 1538, 1029, 846 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$, two diastereomers): δ 8.25-7.96 (m, 18H), 7.61 (m, 2H), 7.44 (m, 4H), 7.21 (dt, *J* = 3.0, 7.5 Hz, 2H), 4.97 and 4.94 (AB spin system, d, *J* = 10.5 Hz, 2H), 4.77 and 4.72 (AB spin system, d, *J* = 14 Hz, 2H), 4.66 (t, *J* = 3.5 Hz, 1H), 4.62 (t, *J* = 3.5 Hz, 1H), 3.84 (m, 2H), 3.50 (m, 2H), 3.26 (m, 4H), 3.02 (m, 2H), 2.75 (m, 2H), 2.36 (s, 6H), 1.82-1.42 (m, 12H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$, two diastereomers): δ 201.9 (C), 139.1 (C), 136.6 (C), 132.2 (C), 131.9 (CH), 131.8 (C), 131.4 (C), 130.2 (CH), 129.1 (CH), 128.6 (CH), 128.50 (CH), 128.53 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 127.2 (CH), 126.5 (CH), 126.3 (CH), 125.8 (C), 124.9 (C), 124.7 (CH), 124.2 (CH), 122.1 (CH), 36.8 (CH_2), 98.6 (CH), 98.5 (CH), 93.8 (C), 67.26 (CH_2), 67.29 (CH_2), 62.4 (CH_2), 34.33 (CH_2), 34.30 (CH_2), 30.58 (CH_2), 30.52 (CH_2), 27.34 (CH_3), 27.31 (CH_3), 25.4 (CH_2), 19.54 (CH_2), 19.48 (CH_2) ppm.

HRMS: M+1 ($C_{33}H_{32}NO_5^+$) 522.2275 calcd; 522.2283 obsd.



4.140 **4.141**

2-Methyl-2-(pyren-1-yl)-5-(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)-3,4-dihydro-*2H*-pyrrole-1-oxide (4.141). To a solution of 4-(3,6-dihydropyren-1-yl)-4-nitro-1-(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)pentan-1-one (**4.140**, 3.883 g, 7.444 mmol) and ammonium chloride (438 mg, 8.19 mmol) in tetrahydrofuran (38 mL) and water (12 mL) was added zinc powder (1.947 g, 29.78 mmol) at 0 °C over 15 minutes. The reaction mixture was allowed to warm to room temperature open to the atmosphere overnight. The mixture was filtered through a celite pad, and rinsed with chloroform. The aqueous layer was extracted with chloroform (2 × 40 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 2.267 g of a fluffy, slightly yellowish solid. The solid was purified by silica gel column chromatography with 1:2 hexanes/ethyl acetate to give 1.957 g (54% yield) of the title compound as a fluffy yellowish solid.

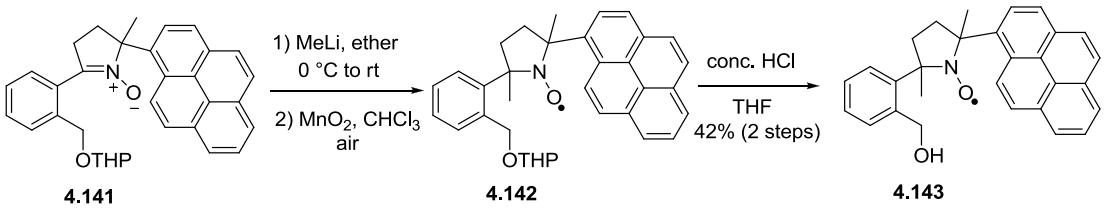
TLC: 1:2 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.30.

IR: ($CDCl_3$) 2941, 1583, 1440, 1199, 1032, 906, 846, 728 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$, two diastereomers): δ 8.43-8.04 (m, 18H), 7.64 (t, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 5.06 and 5.03 (AB spin system, d, *J* = 12.5 Hz, 2H), 4.85 and 4.77 (AB spin system, d, *J* = 12.5 Hz, 2H), 4.27 (t, *J* = 3.5 Hz, 1H), 4.69 (t, *J* = 3.5 Hz, 1H), 3.93 (dt, *J* = 3.0, 8.5 Hz, 2H), 3.55 (m, 2H), 3.33 (m, 2H), 2.98 (m, 4H), 2.78 (m, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 1.91-1.56 (m, 12H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$, two diastereomers): δ 143.4 (C), 138.3 (C), 135.6 (C), 135.5 (C), 130.3 (C), 129.99 (CH), 129.90 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 128.1 (CH), 127.81 (CH), 127.77 (CH), 127.6 (CH), 127.54 (CH), 127.49 (CH), 127.4 (C), 126.2 (CH), 126.0 (C), 125.8 (CH), 125.4 (CH), 125.2 (C), 12514 (CH), 125.10 (CH), 124.9 (CH), 124.15 (CH), 124.12 (CH), 98.3 (CH), 97.9 (CH), 82.6 (C), 68.0 (CH_2), 62.7 (CH_2), 62.3 (CH_2), 36.2 (CH_2), 36.1 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 27.4 (CH_3), 27.3 (CH_3), 25.5 (CH_2), 19.8 (CH_2), 19.5 (CH_2) ppm.

HRMS: M+1 ($C_{33}H_{32}NO_3^+$) 490.2377 calcd; 490.2379 obsd.



4.141 **4.142** **4.143**

2-(2-(Hydroxymethyl)phenyl)-2,5-dimethyl-5-(pyren-1-yl)pyrrolidin-*N*-oxyl (4.143). To a solution of 2-methyl-2-(pyren-1-yl)-5-(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)-3,4-dihydro-*2H*-pyrrole-1-oxide (**4.141**, 1.700 g, 3.472 mmol) in diethyl ether (12 mL) was slowly added a solution of methyllithium (1.6 M in diethyl ether, 21.8 mL, 34.9 mmol) at 0 °C. The ice bath was removed, and the reaction mixture was allowed to stir at room temperature overnight. The next day, the reaction was cooled to 0 °C, and then quenched with saturated ammonium chloride (50 mL). The mixture was diluted with diethyl ether (20 mL) and H_2O (10 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a yellowish solid. The oil was dissolved in chloroform (12 mL), and manganese dioxide (151 mg, 1.74 mmol) was added. Air was bubbled through the solution for one hour. The mixture was filtered through a celite pad, and rinsed with chloroform. The filtrate was concentrated *in vacuo* to give 1.805 g of the crude product **4.142** as an orange oil. The oil was dissolved in tetrahydrofuran (12 mL), and concentrated hydrochloric acid (12 M, 29 μL, 0.348 mmol) was added. The reaction was allowed to stir overnight at room temperature. The next day, saturated

sodium bicarbonate (10 mL) was added. The solution was diluted with dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 1.106 g of a fluffy, yellowish solid. The solid was purified by silica gel column chromatography with 2:1 hexanes/ethyl acetate, followed by 1:1 hexanes/ethyl acetate to give 615 mg (42% yield) of the title compound as a fluffy white solid.

TLC: 2:1 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.44.

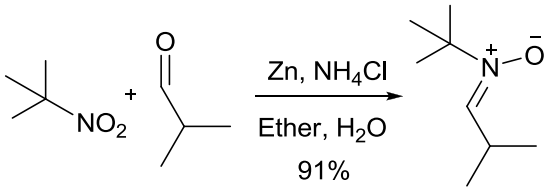
IR: ($CDCl_3$) 3369 (br), 2989, 1601, 1444, 1022, 907, 847, 728 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.60-6.79 (br m, 13H), 5.31-4.76 (br m, 2H), 3.53-2.23 (br m, 4H), 2.11 (s, 3H), 1.90 (s, 3H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 146.8 (C), 144.4 (C), 138.1 (C), 132.0 (CH), 131.6 (C), 130.5 (C), 130.3 (C), 29.3 (CH), 128.1 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 126.4 (CH), 126.2 (C), 126.1 (CH), 125.9 (CH), 125.4 (CH), 125.2 (CH), 124.9 (CH), 124.8 (CH), 124.6 (CH), 64.7 (CH_2), 38.0 (CH_2), 37.4 (CH_2), 26.2 (CH_3), 23.8 (CH_3) ppm.

HRMS: M+1 ($C_{29}H_{28}NO_2^+$) 422.2115 calcd; 422.2121 obsd.

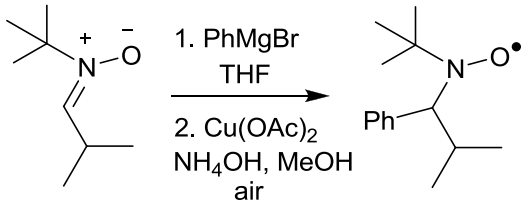
6.4 Experimental Procedures for Chapter 5



5.13

***N-tert*-Butyl-α-isopropylnitrone**[23] **(5.13).** To a solution of 2-methyl-2-nitropropane (2.026 g, 19.65 mmol) and isobutyraldehyde (2.211 g, 30.66 mmol) in water (39mL) and diethyl ether (16mL) chilled in an ice bath was added ammonium chloride (1.199 g, 22.42 mmol). Zinc metal (5.179 g, 79.20 mmol) was added over 15 minutes. The solution was left stirring open to atmosphere at room temperature overnight. The product was filtered through celite pad, and the filter-cake was rinsed with dichloromethane. The aqueous layer was extracted with dichloromethane (4 × 20 mL), and the organic layers were combined, washed with brine (60 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 2.558 g (91% yield) of the title product as a slightly yellowish oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.63 (d, 1H, *J* = 7.20 Hz), 3.18 (m, 1H), 1.48 (s, 9H), 1.10 (d, 6H, *J* = 6.60 Hz) ppm.



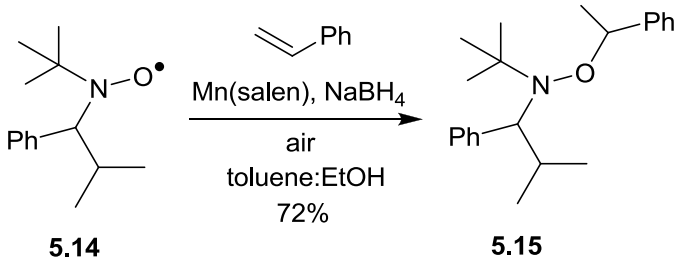
5.13 **5.14**

2,2,5-Trimethyl-4-phenyl-3-azahexane-3-nitroxide[23] **(5.14).** To a solution of *N-tert*-butyl-α-isopropyl nitrone (**5.13**, 2.536 g, 17.70 mmol) in tetrahydrofuran (15 mL) was added a solution of phenylmagnesium bromide (3.0 M, 12 mL, 36 mmol) dropwise at 0 ^{o}C. The solution was allowed to warm to room temperature overnight. Saturated ammonium chloride (3 mL) and water (10 mL) were added into the reaction mixture to quench the excess Grignard reagent and to dissolve the white precipitate. The aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting orange oil was dissolved in methanol (65 mL), and concentrated ammonium hydroxide solution (7.4 M, 4.70 mL, 35 mmol) was added. Then copper acetate (144 mg, 0.721 mmol) was added while bubbling air through the solution for 20 minutes until the solution turned green. Afterwards, the mixture was concentrated *in vacuo*. Chloroform (20 mL), water (20 mL) and saturated sodium bisulfate (5 mL) were added to the reaction mixture. The aqueous layer was extracted with chloroform (2 × 20 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 2.636 g of a brown-

orange oil. The resulting oil was purified by silica gel column chromatography, first with hexanes, then with 95:5 hexane/ethyl acetate, to give 2.307 g (82% yield) of the title product as a bright orange oil.

TLC: 95:5 hexane/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.30.

^{1}H-NMR (600 MHz, $CDCl_3$ addition of $PhNHNH_2$): δ 7.42-6.83 (m, 5H), 3.60 (broad s, partial exchange, 1H), 3.41 (d, 1H, *J* = 9.6 Hz), 2.30 (m, 1H), 0.94 (s, 9H), 1.15 and 0.60 (d, 6H, *J* = 6.6 Hz) ppm.



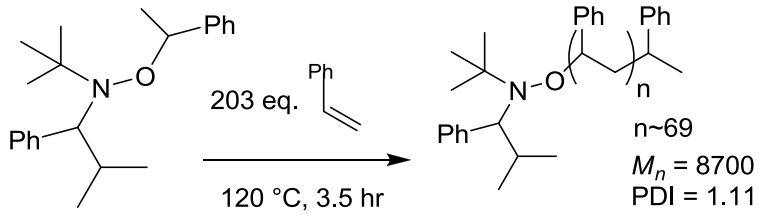
5.14 **5.15**

2,2,5-Trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane[23] **(5.15)**. 2,2,5-Trimethyl-4-phenyl-3-azahexane-3-nitroxide (**5.14**, 1.461 g, 6.631 mmol) was dissolved in 2:3 v/v of toluene (24 mL) and ethanol (34 mL) followed by the addition of styrene (1.473 g, 14.14 mmol). Manganese salen catalyst[5] (470 mg, 1.32 mmol) was then added followed by sodium borohydride (756 mg, 4.60 mmol), and the reaction was allowed to stir open to the atmosphere overnight. The reaction mixture was concentrated and combined with dichloromethane (40 mL), water (40 mL), and a few drops of 10% hydrochloric acid was added (until pH ~ 7) to break the resulting

emulsion. The aqueous layer was extracted three times with dichloromethane (30 mL). The combined organic layer was washed with saturated sodium bicarbonate (100 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 2.962 g of a brownish oil. The resulting oil was purified by silica gel column chromatography with 95:5 hexane/ethyl acetate to give 1.559 g (72% yield) of the title product as a colorless oil.

TLC: 95:5 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.66.

^{1}H-NMR (600 MHz, $CDCl_3$, two diastereomers) δ 7.46-7.02 (m, 20H), 4.93 (q, 1H, *J* = 6.6 Hz), 4.92 (q, 1H, *J* = 6.6 Hz), 3.44 (d, 1H, *J* = 10.8 Hz), 3.32 (d, 1H, *J* = 10.8 Hz), 2.35 (m, 1H), 1.65 (d, 3H, *J* = 6.6 Hz), 1.56 (d, 3H, *J* = 6.6 Hz), 1.40 (m, 1H), 1.32 (d, 3H, *J* = 6.6 Hz), 1.06 (s, 9H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.79 (s, 9H), 0.56 (d, 3H, *J* = 6.6 Hz), 0.24 (d, 3H, *J* = 6.6 Hz) ppm.

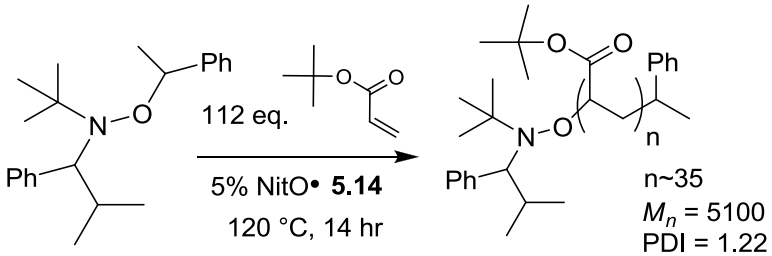


5.15 **5.16**

'69mer' Polystyrene (5.16). Following the procedure of Hawker *et al*,[23] to a 5 mL ampule was added 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (**5.15**, 157 mg, 0.0482 mmol), and styrene monomer (1.019 g, 9.783 mmol). The ampule

was subjected to three freeze/pump/thaw cycles, sealed under argon and heated in an oil bath at 120 °C for 3.5 hours. After cooling, an aliquot was analyzed by ^{1}H-NMR to determine the percent monomer conversion: 34%. The mixture was dissolved in tetrahydrofuran, and methanol was added dropwise to precipitate a white polymer. The polymer was filtered and dried *in vacuo* to afford 367 mg (34% yield) of the title product as a white powder. The GPC trace showed M_n = 8700 amu, PDI = 1.11.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.3-6.9 (br, aromatic H), 6.7-6.3 (br, aromatic H), 2.0-1.7 (br, *PhC<u>H</u>*), 1.7-1.3 (br, *PhCHC<u>H</u>$_2$*) ppm.

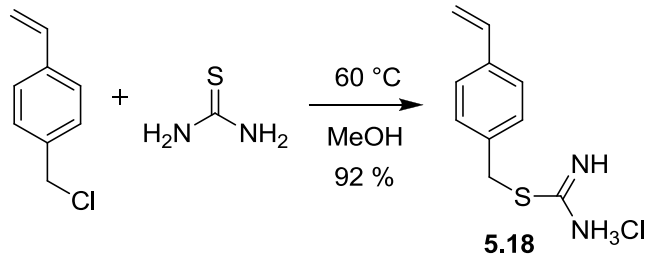


5.15 **5.17**

'35mer' Poly-*tert*-butyl acrylate (5.17). Following the procedure of Hawker *et al*,[23] to a 5 mL ampule was added 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (**5.15**, 265 mg, 0.0814 mmol), 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (**5.14**, 0.1 mg, 0.004 mmol) and *tert*-butyl acrylate monomer (1.165 g, 9.089 mmol). The ampule was subjected to three freeze/pump/thaw cycles, sealed under argon and heated in an oil bath at 120 °C for 14 hours. After cooling, an aliquot was analyzed by ^{1}H-NMR to determine the percent monomer conversion:

31%. The mixture was dissolved in tetrahydrofuran, and then methanol/water (1:1 v/v) was added dropwise to precipitate a white polymer. The polymer was filtered and dried *in vacuo* to afford 286 mg (22% yield) of the title product as a white powder. The GPC trace showed M_n = 5100 amu, PDI = 1.22.

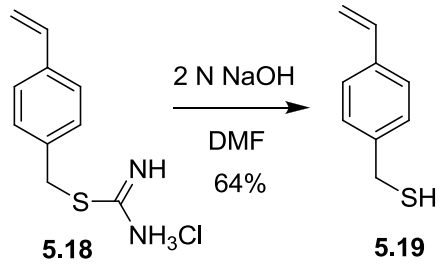
^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.3-2.2 (br, *C<u>H</u>*), 1.9-1.8 and 1.6-1.4 (br, *C<u>H</u>$_2$*), 1.45 (s, *C<u>H</u>$_3$*) ppm.



5.18

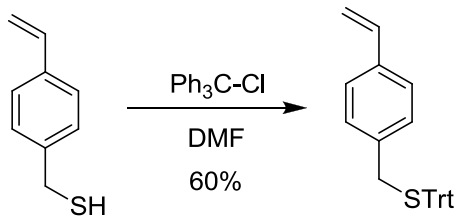
2-(4-Vinyl-benzyl) *iso*thiourea hydrochloride[24] (5.18). Thiourea (3.517 g, 46.20 mmol) was dissolved in methanol (15 mL) in a flask containing 4-vinylbenzyl chloride (7.077 g, 46.37 mmol). The reaction was heated at 60 ^{o}C overnight. Upon colling, diethyl ether was added to the reaction mixture until a constant turbidity was observed; this solution was left in the freezer overnight. The next day, the *iso*thiouronium salt was filtered, and rinsed with diethyl ether to give 9.728 g (92% yield) of the title product as a white powder.

^{1}H-NMR (600 MHz, CD_3OD): δ 7.45 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 6.74 (dd, 1H, *J* = 17.4, 10.8 Hz), 5.81 (dd, 1H, *J* = 17.4, 0.6 Hz), 5.27 (dd, 1H, *J* = 10.8, 0.6 Hz), 4.42 (s, 2H) ppm.



4-Vinyl-phenyl methanethiol[25] **(5.19).** To a 50 mL round bottom flask equipped with a stir bar and purged with nitrogen was added 2-(4-vinyl-benzyl) *iso*thiourea hydrochloride (**5.18**, 3.004 g, 13.13 mmol), dimethylformamide (5 mL, degassed by bubbling with nitrogen) and 2 N sodium hydroxide (15 mL, 30 mmol, degassed by bubbling with nitrogen). The reaction mixture was stirred overnight. To this solution was added 2 N hydrochloric acid (20 mL) to quench the reaction, and the mixture was allowed to stir for 5 minutes. The solution was taken up in diethyl ether (60 mL), washed with water (4 × 50 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 1.260 g (64% yield) of the title product as a yellowish oil. The product was used immediately in the next reaction.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 6.73 (dd, 1H, *J* = 17.5, 10.5 Hz), 5.76 (dd, 1H, *J* = 17.5, 1.0 Hz), 5.26 (dd, 1H, *J* = 10.5, 1.0 Hz), 3.75 (d, 2H, *J* = 7.5 Hz), 1.77 (t, 1H, *J* = 7.5 Hz) ppm.



5.19 **5.20**

(4-Vinyl-benzyl)-trityl sulfide (5.20). 4-Vinyl-phenyl methanethiol (**5.19**, 1.260 g, 8.386 mmol) was dissolved in dimethylformamide (4 mL) followed by the addition of trityl chloride (2.304 g, 8.264 mmol). The reaction mixture was stirred overnight. The mixture was concentrated and purified by silica gel column chromatography with 3:2 hexanes/dichloromethane to afford 1.812 g (60% yield) of the title product as a colorless solid.

TLC: 3:2 hexanes/dichloromethane, UV, *p*-anisaldehyde stain, R_f = 0.65.

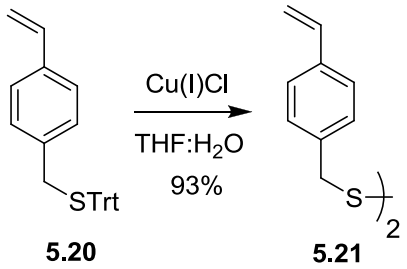
Melting point: 99-100 ^{o}C.

IR: (neat) 3055, 1509, 1488, 1444, 742, 699 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.48-7.09 (m, 19H), 6.67 (dd, *J* = 17.4, 10.8 Hz), 5.70 (dd, 1H, *J* = 17.4, 1.0 Hz), 5.21 (dd, 1H, *J* = 10.8, 1.0 Hz), 1.54 (s, 1H) ppm.

^{13}C-NMR, DEPT (150 MHz, $CDCl_3$): δ 144.7 (C), 136.6 (C), 136.5 (C), 136.4 (CH), 129.6 (CH), 129.3 (CH), 128.0 (CH), 126.7 (CH), 126.4 (CH), 113.7 (CH_2), 67.5 (C), 36.8 (CH_2) ppm.

LRMS: M+1 ($C_{28}H_{25}S^+$) calculated for 393.2 not found; trityl group ($C_{19}H_{15}^+$) 243.1 obsd.



5.20 **5.21**

1, 2-Bis (4-vinyl-benzyl) disulfide (5.21). Following the procedure of Wang *et al*,[26] (4-vinyl-benzyl)-trityl sulfide (**5.20**, 400 mg, 1 mmol) was dissolved in tetrahydrofuran (5 mL) followed by the addition of copper (I) chloride (209 mg, 2.11 mmol) and water (10 µL) as a cosolvent. The reaction was conducted under ultrasonic irradiation open to air for 7 hours, and small amounts of tetrahydrofuran was added regularly to maintain the original volume. The reaction mixture was taken up with dichloromethane (5 mL) and water (5 mL), and then the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layer was dried over

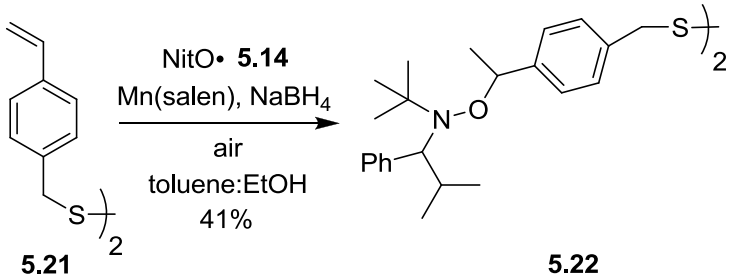
magnesium sulfate, filtered, and concentrated *in vacuo* to give 141 mg (93% yield) of the title product as a yellowish oil.

IR: (neat) 1445, 759, 699, 638 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38-7.20 (m, 8H), 6.71 (dd, 1H, *J* = 17.4, 10.8 Hz), 5.75 (dd, 1H, *J* = 17.4, 2.4 Hz), 5.25 (dd, 1H, *J* = 10.8, 2.4 Hz), 3.63 (s, 1H) ppm.

^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 146.8 (C), 136.9 (C), 136.4 (CH), 129.6 (CH), 127.9 (CH), 127.2(CH), 126.4 (CH), 114.0 (CH_2), 43.1 (CH_2) ppm.

LRMS: M+1 ($C_{18}H_{19}S_2^+$) calculated for 299.1 not found.



5.21 **5.22**

***N*-*tert*-Butyl-*O*-{1-[4-(4-{1-[*N*-*tert*-butyl-*N*-(2-methyl-1-phenyl-propyl)-aminooxy] ethyl}-benzyldisulfanylmethyl)-phenyl]-ethyl}-*N*-(2-methyl-1-phenyl-propyl)-hydroxylamine[27] (5.22).** Following a modified procedure of Hawker *et al*,[28] 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (**5.14**, 72 mg, 0.33 mmol) was dissolved in 2:3 v/v of toluene (0.45 mL) and ethanol (0.65 mL) followed by the addition of 4-vinyl benzyl disulfide (**5.21**, 38 mg, 0.13 mmol). Manganese salen catalyst[5] (11 mg, 0.030 mmol) was then added followed by sodium borohydride (22 mg, 0.58 mmol),

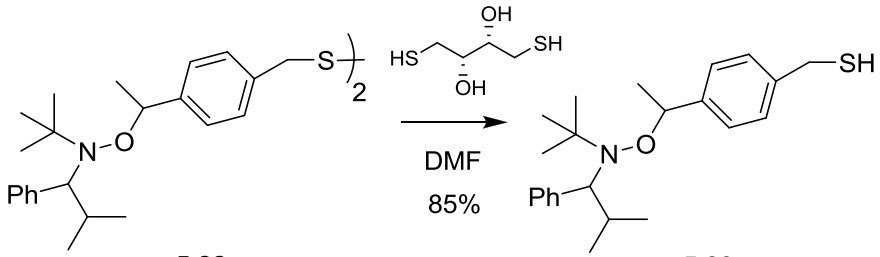
and the reaction was allowed to stir open to the atmosphere overnight. The reaction mixture was concentrated and combined with dichloromethane (10 mL), water (10 mL), and a few drops of 10% hydrochloric acid was added (until pH~7) to break the resulting emulsion. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with saturated sodium bicarbonate (30 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 64 mg of a brownish oil. The resulting oil was purified by silica gel column chromatography with 3:2 hexane/dichloromethane to give 39 mg (41% yield) of the title product as a yellowish oil.

TLC: 3:2 hexanes/dichloromethane, UV, *p*-anisaldehyde stain, R_f = 0.52.

^{1}H-NMR (600 MHz, $CDCl_3$, two diastereomers): δ 7.48-7.12 (m, 36H), 4.91 (q+q, 4H, *J* = 6.6 Hz), 3.68 (s, 4H), 3.57 (s, 2H), 3.56 (s, 2H), 3.42 (d, 1H, *J* = 10.8 Hz), 3.40 (d, 1H, *J* = 10.8 Hz), 3.31 (d, 1H, *J* = 10.8 Hz), 3.30 (d, 1H, *J* = 10.8 Hz), 2.34 (m, 2H), 1.62 (d, 3H, *J* = 6.6 Hz), 1.61 (d, 3H, *J* = 6.6 Hz), 1.54 (d, 3H, *J* = 6.6 Hz), 1.53 (d, 3H, *J* = 6.6 Hz), 1.40 (m, 2H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.30 (d, 3H, *J* = 6.6 Hz), 1.06 (s, 9H), 1.05 (s, 9H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 0.76 (s, 9H), 0.75 (s, 9H), 0.56 (d, 3H, *J* = 6.6 Hz), 0.55 (d, 3H, *J* = 6.6 Hz), 0.21 (d, 3H, *J* = 6.6 Hz), 0.20 (d, 3H, *J* = 6.6 Hz) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ 145.2, 145.1, 144.3, 144.2, 142.4, 142.2, 136.3, 136.2, 135.8, 135.6, 131.0, 130.9, 129.2, 127.4, 127.2, 127.1, 126.3, 126.2, 126.1, 83.3,

82.5, 82.4, 72.2, 60.5, 60.4, 43.2, 43.1, 43.0, 32.1, 31.7, 28.4, 28.2, 24.8, 24.7, 23.3, 23.2, 22.2, 22.0, 21.2, 21.1 ppm.

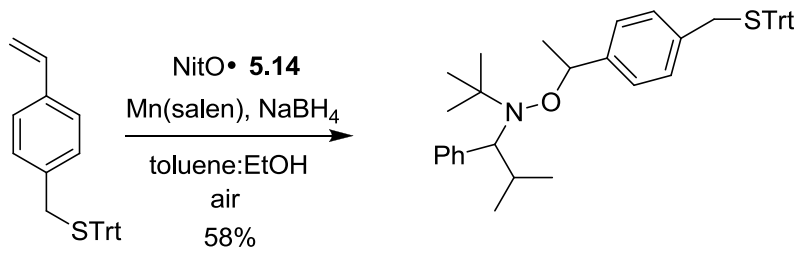


5.22 **5.23**

***N*-*tert*-Butyl-*O*-[1-(4-mercaptomethyl-phenyl)-ethyl]-*N*-(2-methyl-1-phenyl-propyl)-hydroxylamine[27] (5.23).** Following the procedure of Braslau *et al*,[27] disulfide initiator (**5.22**, 95 mg, 0.13 mmol) was dissolved in dimethylformamide (2 mL) followed by the addition of dithiothreitol (DTT, 41 mg, 0.27 mmol). The reaction flask was subjected to three freeze/pump/thaw cycles and stirred at 60 ^{o}C overnight. Upon cooling, the reaction mixture was taken up in dichloromethane (10 mL), washed five times with water (10 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 40 mg (85% yield) of the title product as a yellowish oil.

^{1}H-NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.50-7.10 (m, 18H), 4.89 (q+q, 2H, *J* = 6.5 Hz), 3.75 (d, 2H, *J* = 7.5 Hz), 3.72 (d, 2H, *J* = 7.5 Hz), 3.41 (d, 1H, *J* = 10.5 Hz), 3.29 (d, 1H, *J* = 10.5 Hz), 2.30 (m, 1H), 1.74 (td, 2H, J_t = 7.5 Hz, J_d = 2.5 Hz), 1.60 (d,

3H, *J* = 6.5 Hz), 1.52 (d, 3H, *J* = 6.5 Hz), 1.40 (m, 1H), 1.29 (d, 3H, *J* = 6.5 Hz), 1.03 (s, 9H), 0.91 (d, 3H, *J* = 6.5 Hz), 0.77 (s, 9H), 0.52 (d, 3H, *J* = 6.5 Hz), 0.21 (d, 3H, *J* = 6.6 Hz) ppm.



5.20 **5.24**

***N*-[1-(4-Tritylthiomethyl-phenyl)-ethoxy]-*N*-*tert*-butyl-2-methyl-1-phenylpropan-1-amine (5.24).** Following a modified procedure of Hawker *et al*,[28] 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (**5.14**, 43 mg, 0.20 mmol) was dissolved in 2:3 v/v of toluene (0.70 mL) and ethanol (0.95 mL) followed by the addition of (4-vinyl-benzyl)-trityl sulfide (**5.20**, 150 mg, 0.38 mmol). Manganese salen catalyst[5] (17 mg, 0.048 mmol) was then added followed by sodium borohydride (23 mg, 0.61 mmol) and the reaction was allowed to stir open to the atmosphere overnight. The reaction mixture was concentrated and combined with dichloromethane (10 mL), water (10 mL), and a few drops of 10% hydrochloric acid was added (until pH~7) to break the resulting emulsion. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The

combined organic layer was washed with saturated sodium bicarbonate (30 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 231 mg of a brownish oil. The resulting oil was purified by silica gel column chromatography with 3:2 hexanes/dichloromethane to give 69 mg (58% yield) of the title product as a white solid.

TLC: 3:2 hexanes/dichloromethane, UV, *p*-anisaldehyde stain, R_f = 0.67.

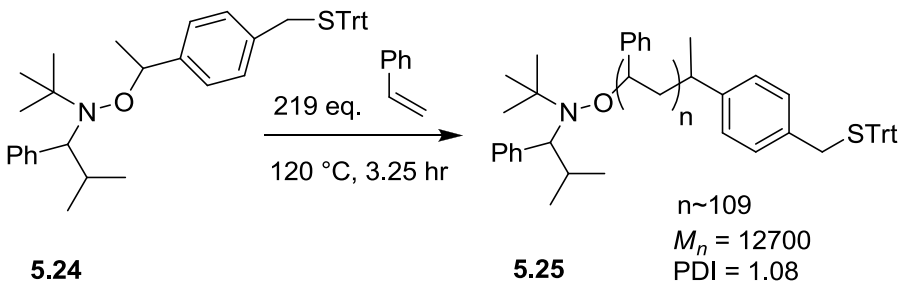
Melting point: 62-63 ^{o}C.

IR: (neat) 2973, 1489, 1444, 1361, 1206, 1061, 740, 700 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$, diastereomers): δ 7.50-7.07 (m, 40H), 4.87 (q+q, 2H, *J* = 6.6 Hz), 3.40 (d, 1H, *J* = 10.8 Hz), 3.33 (s, 2H), 3.29 (s, 2H), 3.29 (d, 1H, *J* = 10.8 Hz), 2.32 (m, 1H), 1.58 (d, 3H, *J* = 6.6 Hz), 1.51 (d, 3H, *J* = 6.6 Hz), 1.37 (m, 1H), 1.29 (d, 3H, *J* = 6.6 Hz), 1.03 (s, 9H), 0.91 (d, 3H, *J* = 6.6 Hz), 0.76 (s, 9H), 0.54 (d, 3H, *J* = 6.6 Hz), 0.22 (d, 3H, *J* = 6.6 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$, two diastereomers): δ 144.8, 144.7, 143.9, 142.5, 142.4, 135.9, 135.2, 131.0, 131.0, 129.7, 128.9, 128.9, 128.0, 127.4, 127.3, 127.2, 126.8, 126.4, 126.3, 126.2, 83.2, 82.4, 72.1, 67.4, 60.5, 60.4, 59.3, 36.8, 36.8, 32.0, 31.6, 28.3, 28.2, 24.6, 23.1, 22.1, 21.9, 21.1, 21.0 ppm.

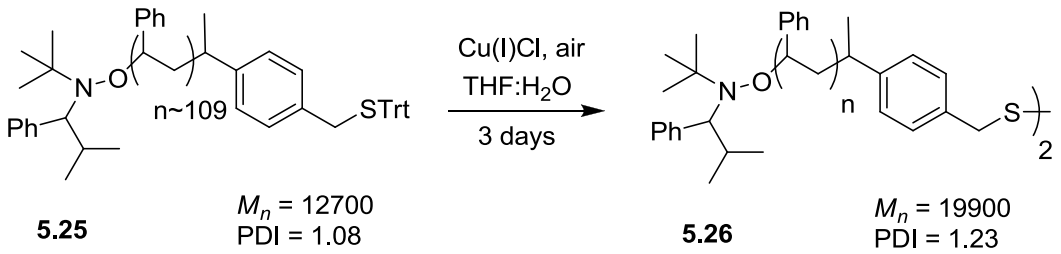
HRMS: M+1 ($C_{42}H_{48}NOS^{+}$) 614.3451 calcd; 614.3436 obsd.



5.24 **5.25**

'109mer' Trityl-protected thiol terminated polystyrene (5.25). Following the procedure of Hawker *et al*,[23] to a 5 mL ampule was added *N*-[1-(4-tritylthiomethyl-phenyl)-ethoxy]-*N*-*tert*-butyl-2-methyl-1-phenylpropan-1-amine (**5.24**, 25 mg, 0.040 mmol), and styrene monomer (913 mg, 8.77 mmol). The ampule was subjected to three freeze/pump/thaw cycles, sealed under argon and heated in an oil bath at 120 ^{o}C for 3.25 hours. After cooling, an aliquot was analyzed by ^{1}H-NMR to determine the percent monomer conversion: 52%. The reaction mixture was dissolved in tetrahydrofuran, and methanol was added dropwise to precipitate a white polymer. The polymer was filtered and dried *in vacuo* to afford 480 mg (50% yield) of the title product as a white powder. The GPC trace showed M_n = 12700 amu, PDI = 1.08.

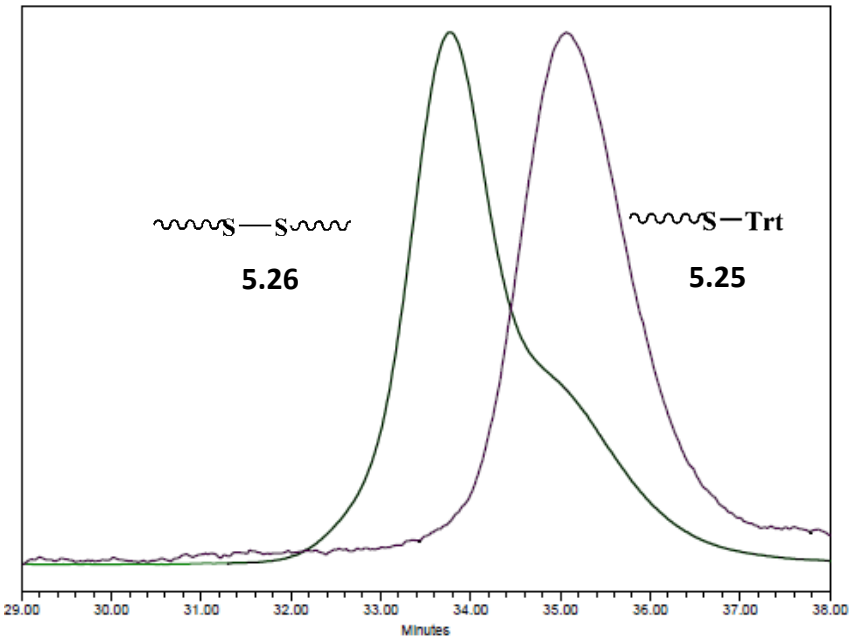
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.2-6.9 (br, aromatic H), 6.7-6.3 (br, aromatic H), 2.0-1.7 (br, *PhC<u>H</u>*), 1.7-1.3 (br, *PhCHC<u>H₂</u>*) ppm.



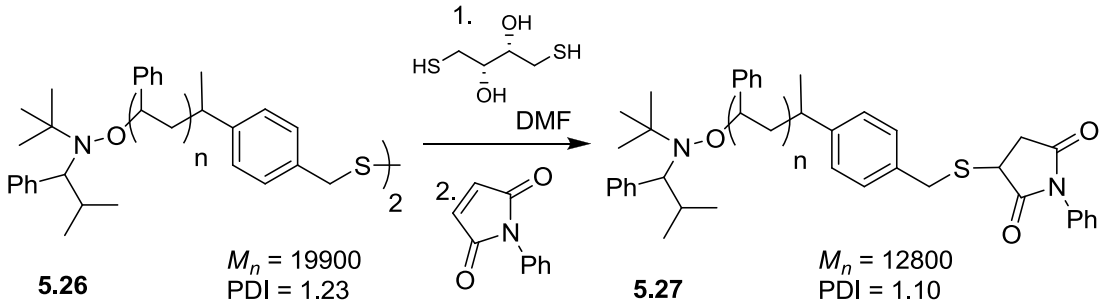
5.25 M_n = 12700, PDI = 1.08

5.26 M_n = 19900, PDI = 1.23

Central disulfide polystyrene (5.26). Following the procedure of Wang *et al*,[26] trityl-protected thiol terminated polystyrene (**5.25**, 100 mg, 0.8 mmol) was dissolved in tetrahydrofuran (2 mL) followed by the addition of copper (I) chloride (22 mg, 0.22 mmol) and water (0.1 mL) as a co-solvent. The reaction was conducted under ultrasonic irradiation open to the atmosphere for 3 days. Tetrahydrofuran was added regularly to maintain the original volume; and the reaction flask was capped each night without ultrasonication. The reaction mixture was taken up in dichloromethane (5 mL) and water (5 mL), and then the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 89 mg of a yellowish powder as a mixture of starting material and product. The GPC trace showed M_n = 19900 amu, PDI = 1.23.

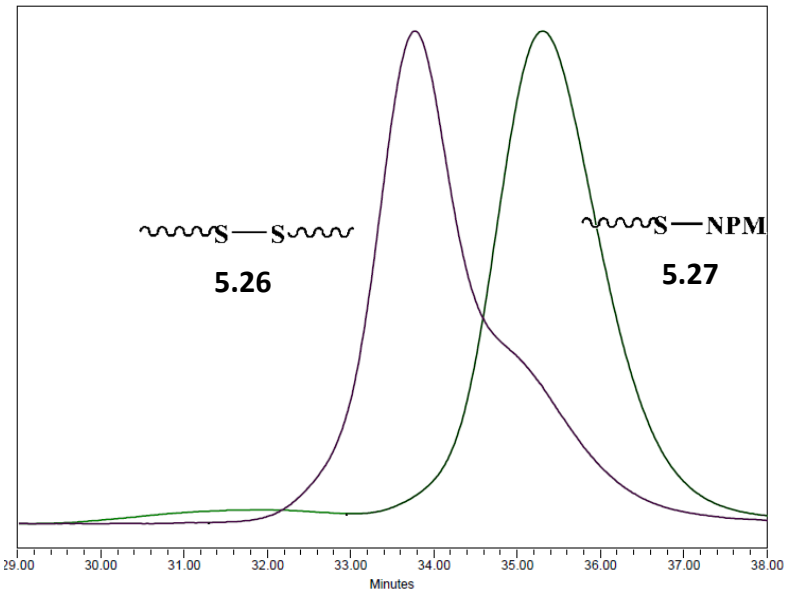


Overlay of GPC chromatographs of trityl-protected polystyrene **5.25** (right, M_n = 12 700, PDI = 1.08) and the resulting disulfide linked polystyrene **5.26** (left, M_n = 19 900, PDI = 1.23)

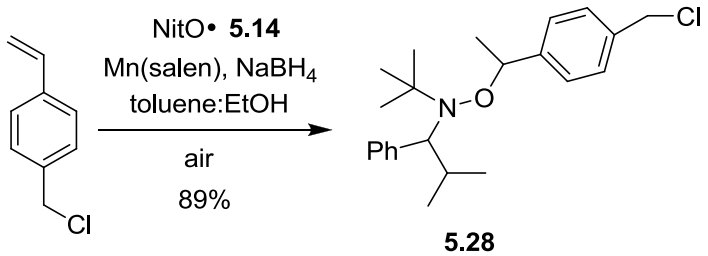


***N*-Phenylmaleimide sulfide terminated polystyrene (5.27).** Following the procedure of Hill *et al.*,[27] central disulfide polystyrene (**5.26**, 26 mg, 0.0010 mmol) was dissolved in dimethylformamide (3 mL) followed by the addition of dithiothreitol

(DTT, 25 mg, 0.16 mmol). The reaction flask was subjected to three freeze/pump/thaw cycles and then heated at 60 ^{o}C for 2 days. After cooling, *N*-phenylmaleimide (34 mg, 0.20 mmol) was added, and the reaction mixture was stirred for an additional 7 hours. The solution was taken up in tetrahydrofuran (1 mL), and methanol was added dropwise to precipitate a white polymer. The polymer was collected by centrifugation to afford 15 mg of a white powder. The GPC trace showed M_n = 16600 amu, PDI = 1.24. There was a small shoulder of high molecular weight polymer in GPC trace, so the polymer was subjected to further reduction using the same conditions for 2 additional days. The resulting GPC trace showed no shoulder: M_n = 12800 amu, PDI = 1.10.



Overlay of GPC chromatographs for disulfide linked polystyrene **5.26** (left, M_n = 19 900, PDI = 1.23) and maleimide-trapped thiol terminated polystyrene **5.27** following disulfide cleavage (right, M_n = 12 800, PDI = 1.10)

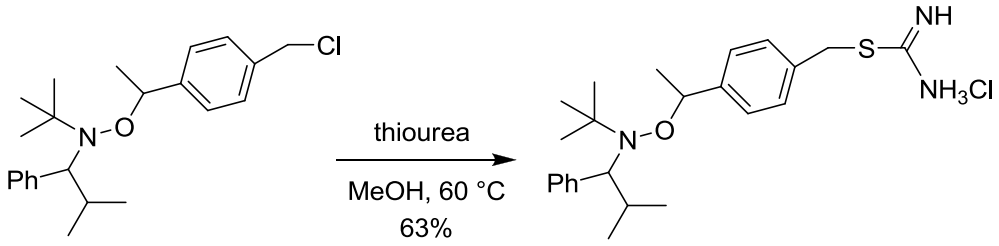


5.28

***N*-[1-(4-(Chloromethyl-phenyl)-ethoxy]-*N*-*tert*-butyl-2-methyl-1-phenylpropan-1-amine**[28] **(5.28).** 2,2,5-Trimethyl-4-phenyl-3-azahexane-3-nitroxide (**5.14**, 935 mg, 4.24 mmol) was dissolved in 2:3 v/v of toluene (15 mL) and ethanol (21 mL) followed by the addition of 4-vinyl benzyl chloride (1.527 g, 9.005 mmol). Manganese salen catalyst[5] (472 mg, 1.32 mmol) was then added followed by sodium borohydride (482 mg, 12.7 mmol), and the reaction was allowed to stir open to the atmosphere overnight. The reaction mixture was concentrated and combined with dichloromethane (20 mL), water (20 mL), and a few drops of 10% hydrochloric acid was added (until pH~7) to break the resulting emulsion. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layer was washed with saturated sodium bicarbonate (45 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 1.821 g of a brownish oil. The resulting oil was purified by silica gel column chromatography with 10:1 hexanes/ethyl acetate to give 1.413 g (89% yield) of the title product as a colorless oil.

TLC: 10:1 hexane/ethyl acetate, UV, *p*-anisaldehyde stain, R_f = 0.28.

^{1}H-NMR (600 MHz, $CDCl_3$, both diastereomers): δ 7.44-7.15 (m, 18H), 4.92 (q+q, 2H, *J* = 6.6 Hz), 4.61 (s, 2H), 4.58 (s, 2H), 3.42 (d, 1H, *J* = 10.8 Hz), 3.30 (d, 1H, *J* = 10.8 Hz), 2.32 (m, 1H), 1.62 (d, 3H, *J* = 6.6 Hz), 1.54 (d, 3H, *J* = 6.6 Hz), 1.38 (m, 2H), 1.30 (d, 3H, *J* = 6.6 Hz), 1.04 (s, 9H), 0.92 (d, 3H, *J* = 6.6 Hz), 0.78 (s, 9H), 0.54 (d, 3H, *J* = 6.6 Hz), 0.23 (d, 3H, *J* = 6.6 Hz) ppm.

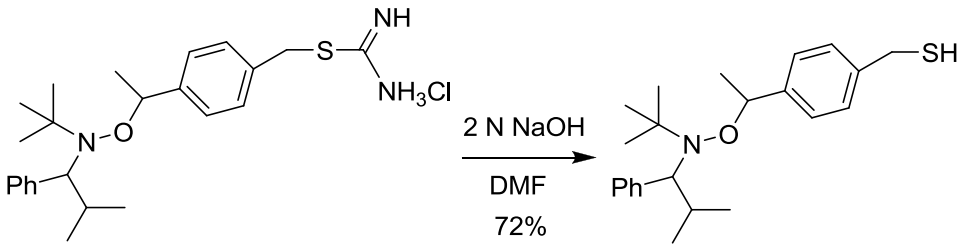


5.28 **5.29**

2-(3-{1-[*N*-*Tert*-butyl-*N*-(methyl-1-phenylpropyl)-aminooxy]-ethyl}-benzyl)-*iso*thiourea hydrochloride[27] **(5.29).** Thiourea (162 mg, 2.13 mmol) was dissolved in methanol (93 mL) in a flask containing *N*-[1-(4-(chloromethyl-phenyl)-ethoxy]-*N*-*tert*-butyl-2-methyl-1-phenylpropan-1-amine (**5.28**, 489 mg, 1.31 mmol). The reaction was heated at 60 ^{o}C overnight. The system was cooled, and the volatiles were removed *in vacuo*. The crude thiouronium salt was purified via flash chromatography with 10:1 ethyl acetate/methanol, followed by 9:1 ethyl acetate/methanol, resulting in 370 mg (63% yield) of a white powder.

TLC: 10:1 ethyl acetate/methanol, UV, *p*-anisaldehyde stain, R_f = 0.33.

^{1}H-NMR (600 MHz, CD_3OD, diastereomers): δ 7.51-7.12 (m, 18H), 4.94 (q+q, 2H, *J* = 6.6 Hz), 4.88 (broad s, 4H), 4.45 (s, 2H), 4.41 (s, 2H), 3.49 (d, 1H, *J* = 10.8 Hz), 3.34 (d, 1H, *J* = 10.8 Hz), 2.37 (m, 1H), 1.63 (d, 3H, *J* = 6.6 Hz), 1.54 (d, 3H, *J* = 6.6 Hz), 1.33 (d, 3H, *J* = 6.6 Hz), 1.31 (m, 1H), 1.06 (s, 9H), 0.91 (d, 3H, *J* = 6.6 Hz), 0.78 (s, 9H), 0.55 (d, 3H, *J* = 6.6 Hz), 0.19 (d, 3H, *J* = 6.6 Hz) ppm.



5.29 **5.23**

***N*-*tert*-Butyl-*O*-[1-(4-mercaptomethyl-phenyl)-ethyl]-*N*-(2-methyl-1-phenyl-propyl)-hydroxylamine**[27] **(5.23).** To a 50 mL round bottom flask equipped with a stir bar and purged with nitrogen was added 2-(3-{1-[*N*-*tert*-butyl-*N*-(methyl-1-phenylpropyl)-aminooxy]-ethyl}-benzyl)-*iso*thiourea hydrochloride (**5.29**, 938 mg, 2.08 mmol), dimethylformamide (11.80 mL, degassed by bubbling with nitrogen) and 2 N sodium hydroxide (8.60 mL, 17.2 mmol, degassed by bubbling with nitrogen). The reaction mixture was stirred at room temperature overnight. To this solution was added 2 N hydrochloric acid (11.80 mL) to quench the reaction, and the mixture was allowed to stir for 30 minutes. The solution was taken up in dichloromethane (25 mL) and water

(25 mL), and then the aqueous layer was extracted with dichloromethane (25 mL). The combined organic layer was washed with distilled water (3 × 25 mL) and once with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 554 mg (72% yield) of the title product as a yellowish oil.

^{1}H-NMR spectrum was identical to **5.23** prepared by DTT cleavage of disulfide **5.22**.

6.5 References

1. Choudary, B. M.; Kantam, M. L.; Bharathi, B.; Reddy, C. R. V., *Journal of Molecular Catalysis A-Chemical* **2001,** *168* (1-2), 69-73.

2. Boeckman, R. K.; Shao, P.; Mullins, J. J., *Organic Syntheses* **2000,** *77*, 141.

3. Clark, J. H.; Miller, J. M.; So, K. H., *Journal of the Chemical Society-Perkin Transactions 1* **1978,** (9), 941-946.

4. Delpierre, G. R.; Lamchen, M., *Journal of the Chemical Society* **1963,** (OCT), 4693-4701.

5. Singh, C.; Srivastav, N. C.; Puri, S. K., *Bioorganic & Medicinal Chemistry* **2004,** *12* (22), 5745-5752.

6. Bushmakina, N. G.; Misharin, A. Y., *Synthesis-Stuttgart* **1986,** (11), 966-966.

7. Yao, S.; Schafer-Hales, K. J.; Cohanoschi, I.; Hernandez, F. E.; Belfield, K. D., *Synlett* **2006,** (12), 1863-1866.

8. Tao, L.; Geng, J.; Chen, G. J.; Xu, Y. J.; Ladmiral, V.; Mantovani, G.; Haddleton, D. M., *Chemical Communications* **2007,** (33), 3441-3443.

9. Benoit, D.; Harth, E.; Fox, P.; Waymouth, R. M.; Hawker, C. J., *Macromolecules* **2000,** *33* (2), 363-370.

10. Reiss, P.; Bleuse, J.; Pron, A., *Nano Letters* **2002,** *2* (7), 781-784; Zaitseva, N.; Dai, Z. R.; Leon, F. R.; Krol, D., *Journal of the American Chemical Society* **2005,** *127* (29), 10221-10226.

11. Yu, W. W.; Qu, L. H.; Guo, W. Z.; Peng, X. G., *Chemistry of Materials* **2003,** *15* (14), 2854-2860.

12. Nyfeler, E.; Renaud, P., *Organic Letters* **2008,** *10* (5), 985-988.

13. Ryu, J. H.; Jeong, J. H., *Archives of Pharmacal Research* **1999,** *22* (6), 585-591.

14. Huang, P. Q.; Zheng, X.; Deng, X. M., *Tetrahedron Letters* **2001,** *42* (51), 9039-9041.

15. Kornblum, N.; Wade, P. A., *Journal of Organic Chemistry* **1973,** *38* (7), 1418-1420.

16. Hernandez, E.; Soderquist, J. A., *Organic Letters* **2005,** *7* (24), 5397-5400.

17. Morris, J. C.; McMurtrie, J. C.; Bottle, S. E.; Fairfull-Smith, K. E., *Journal of Organic Chemistry* **2011,** *76* (12), 4964-4972.

18. Acharya, H. P.; Miyoshi, K.; Kobayashi, Y., *Organic Letters* **2007,** *9* (18), 3535-3538.

19. Eames, J.; Coumbarides, G. S.; Suggate, M. J.; Weerasooriya, N., *European Journal of Organic Chemistry* **2003,** (4), 634-641.

20. Kuang, G. C.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Zhu, L., *Journal of Organic Chemistry* **2010,** *75* (19), 6540-6548.

21. Palmer, A. M.; Chrismann, S.; Munch, G.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Senn-Bilfinger, J.; Feth, M. P.; Simon, W. A., *Bioorganic & Medicinal Chemistry* **2009,** *17* (1), 368-384.

22. Castro, B.; Selve, C., *Bulletin De La Societe Chimique De France* **1971,** (6), 2296-2298.

23. Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J., *Journal of the American Chemical Society* **1999,** *121* (16), 3904-3920.

24. Watanabe, S.; Nakahama, S.; Yamaguchi, K., *Makromolekulare Chemie-Macromolecular Chemistry and Physics* **1991,** *192* (8), 1891-1902.

25. Yamaguchi, K.; Kato, T.; Hirao, A.; Nakahama, S., *Makromolekulare Chemie-Rapid Communications* **1987,** *8* (4), 203-207.

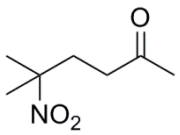
26. Ma, M.; Zhang, X.; Peng, L. L.; Wang, J. B., *Tetrahedron Letters* **2007,** *48* (7), 1095-1097.

27. Hill, N. L.; Jarvis, J. L.; Pettersson, F.; Braslau, R., *Reactive & Functional Polymers* **2008,** *68* (1), 361-368.

28. Dao, J.; Benoit, D.; Hawker, C. J., *Journal of Polymer Science Part A-Polymer Chemistry* **1998,** *36* (12), 2161-2167.

Appendix: NMR Spectra

Note: All nitroxides have been reduced with phenyl hydrazine



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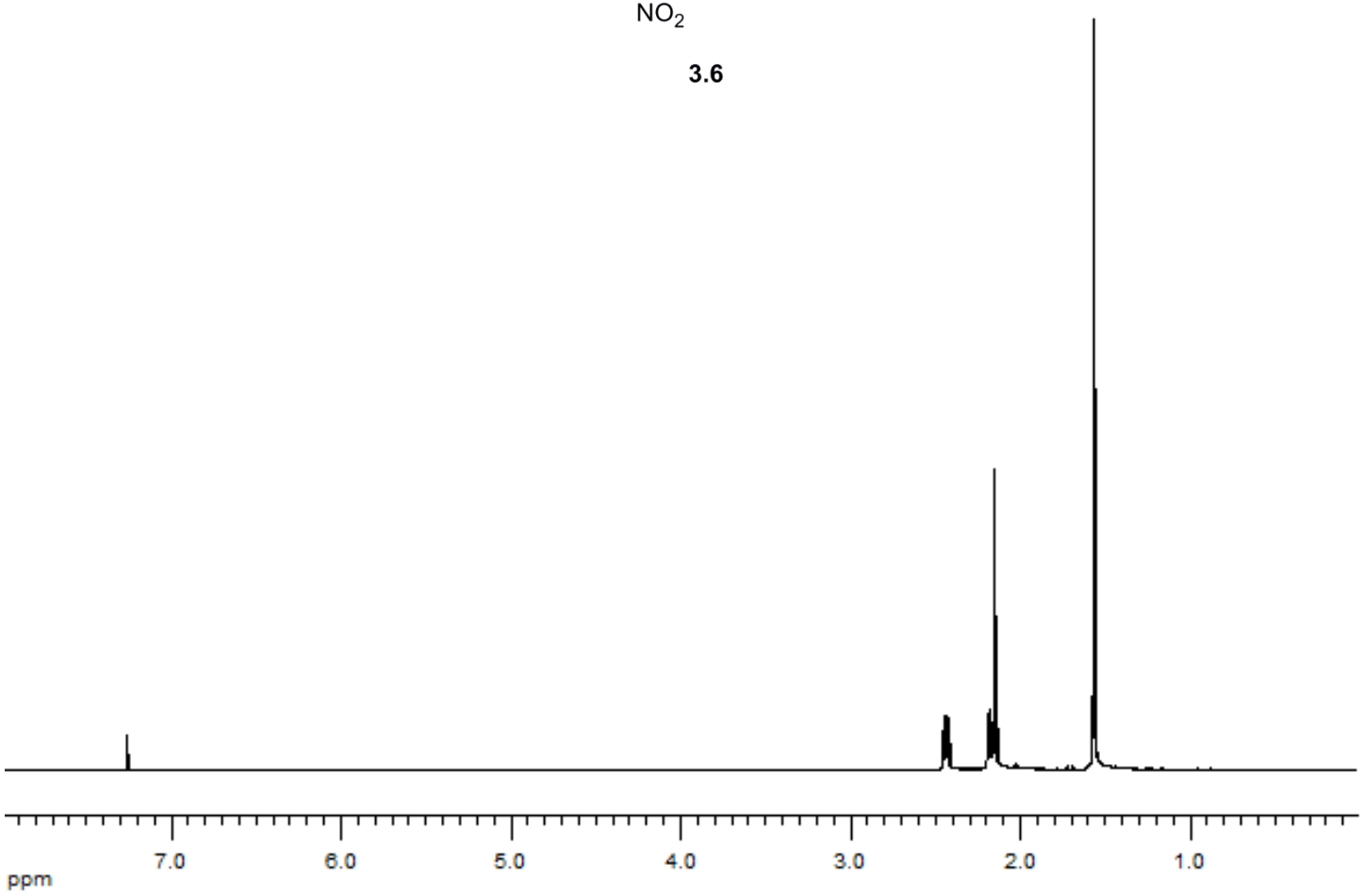

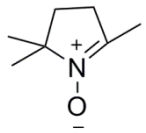

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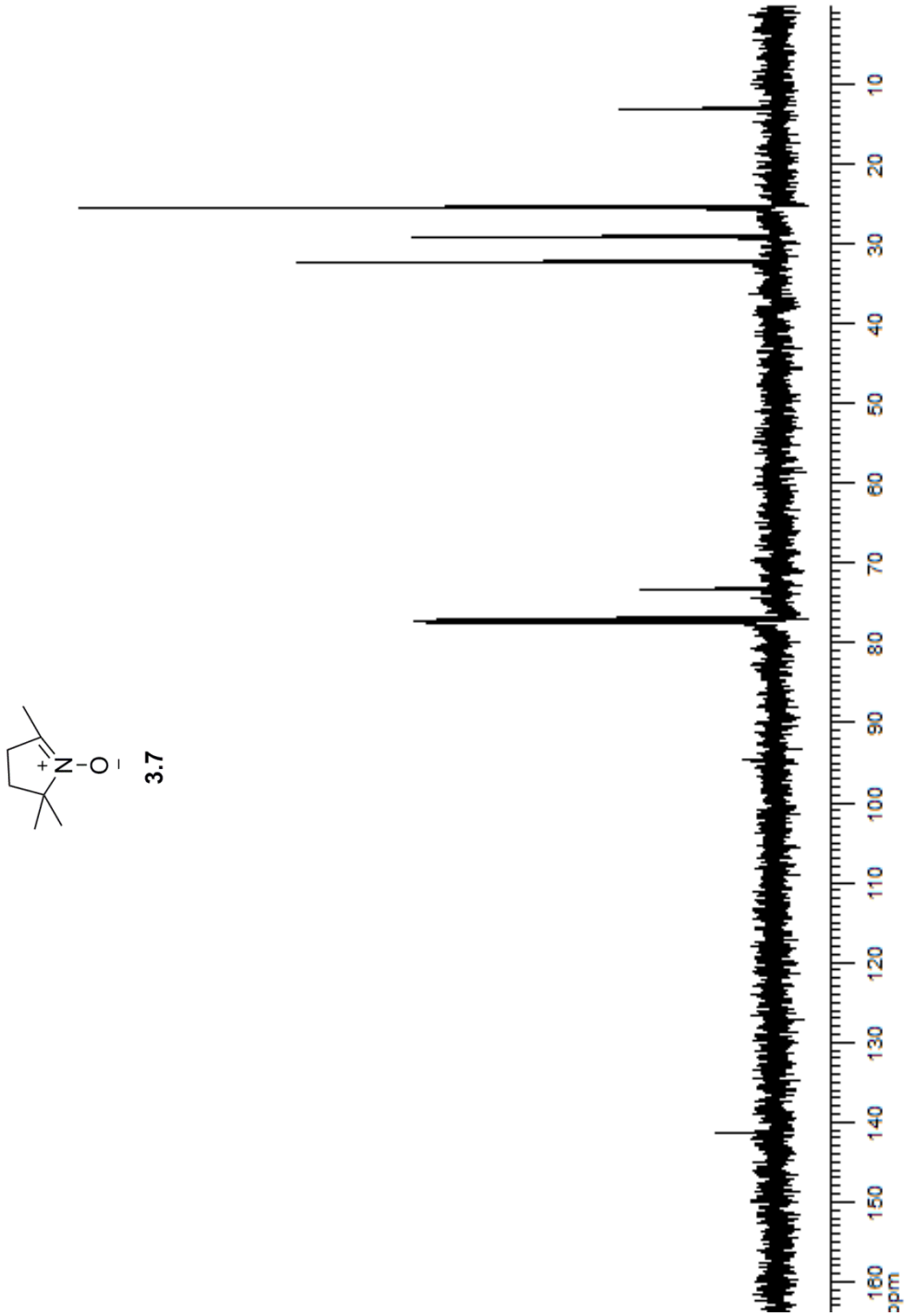
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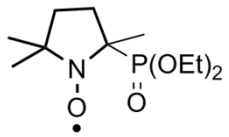

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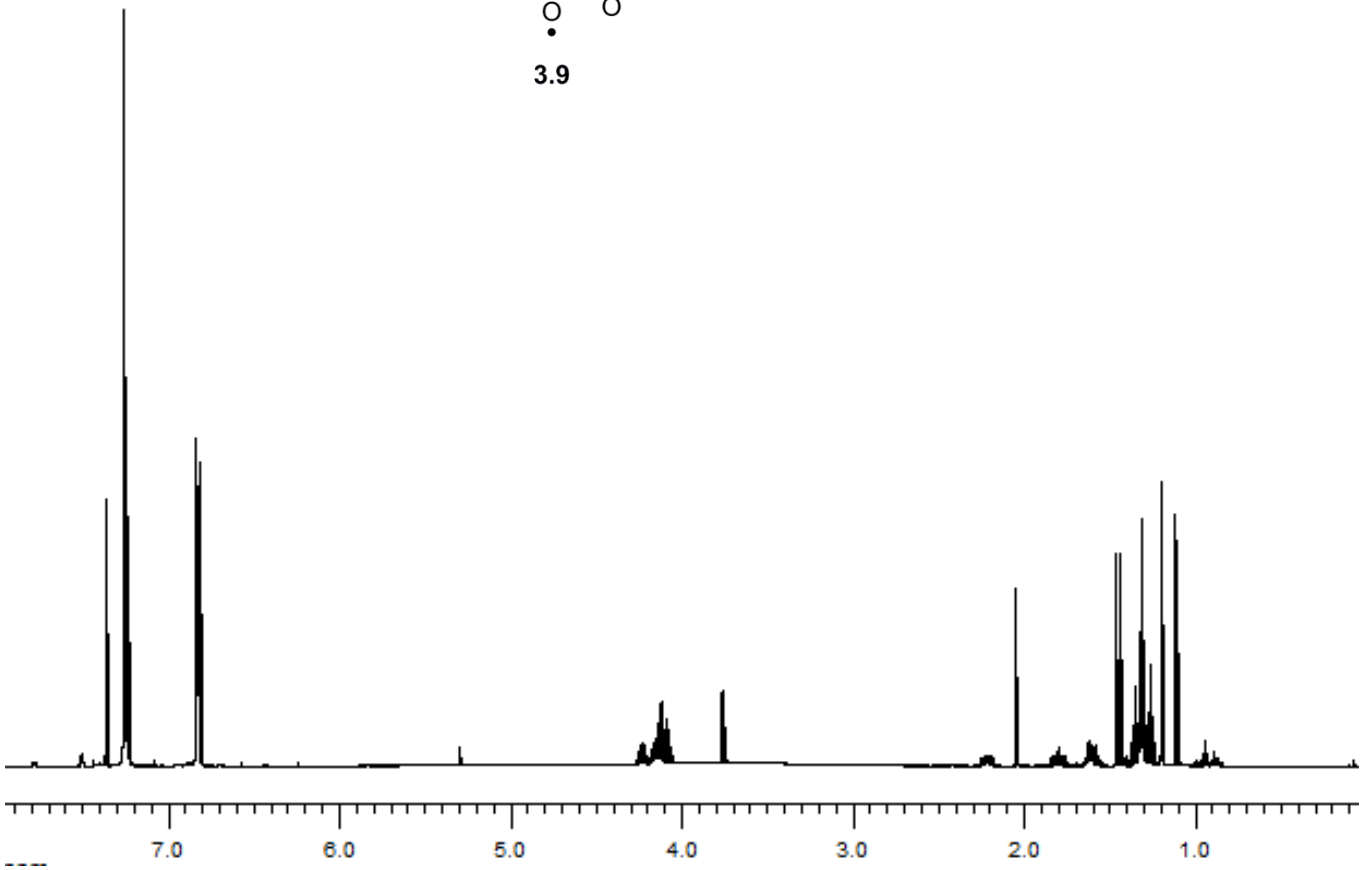

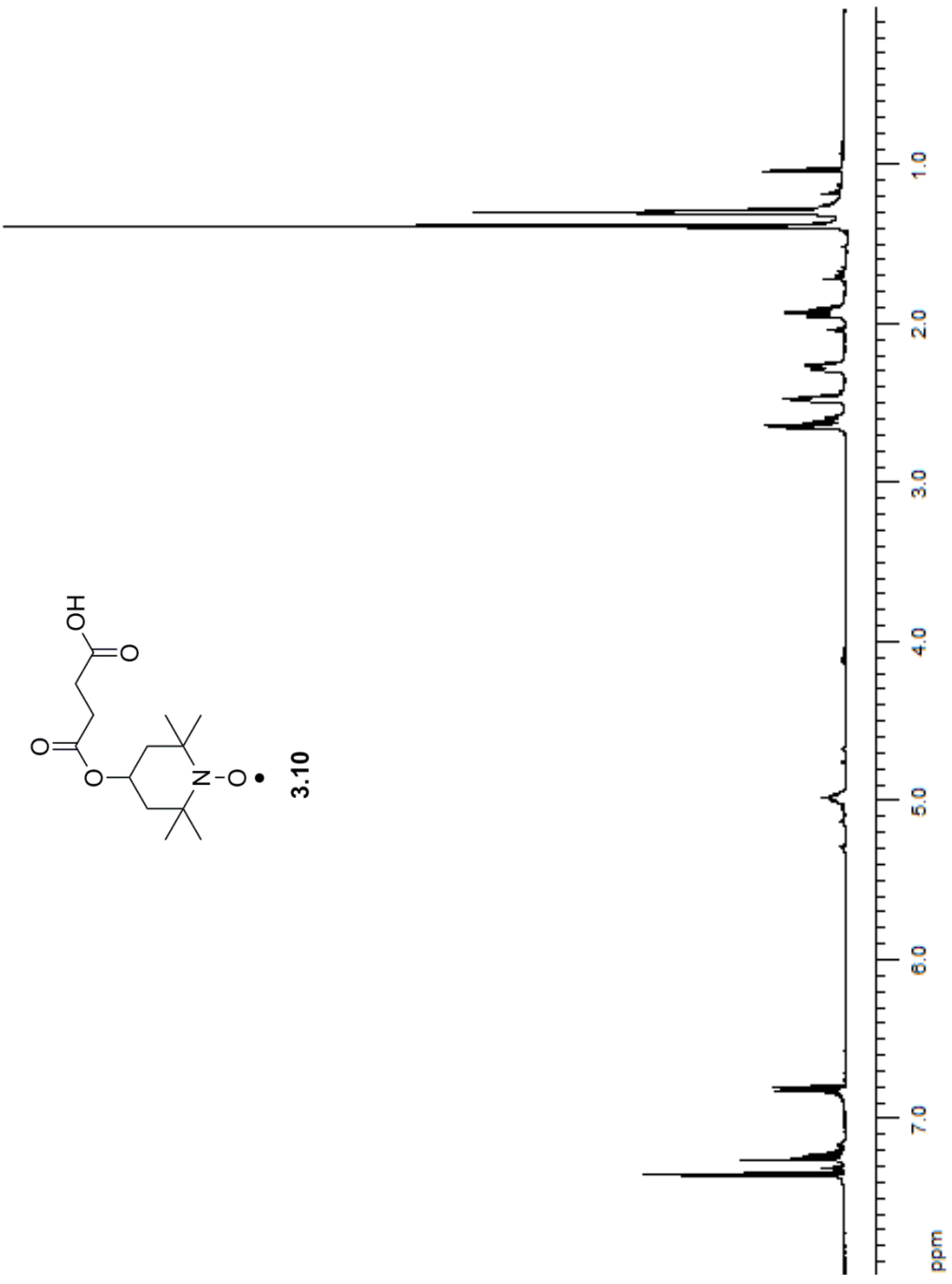
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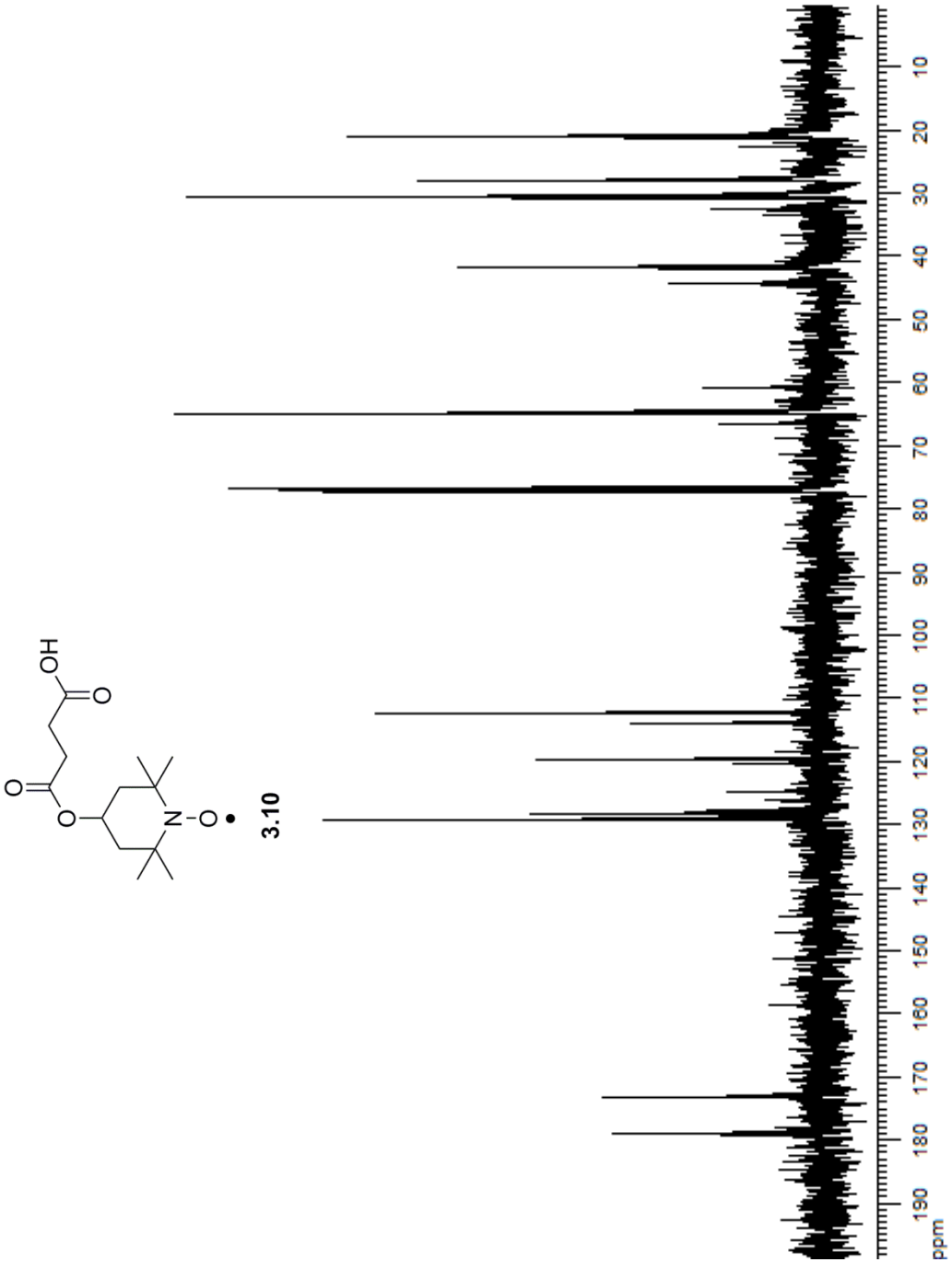
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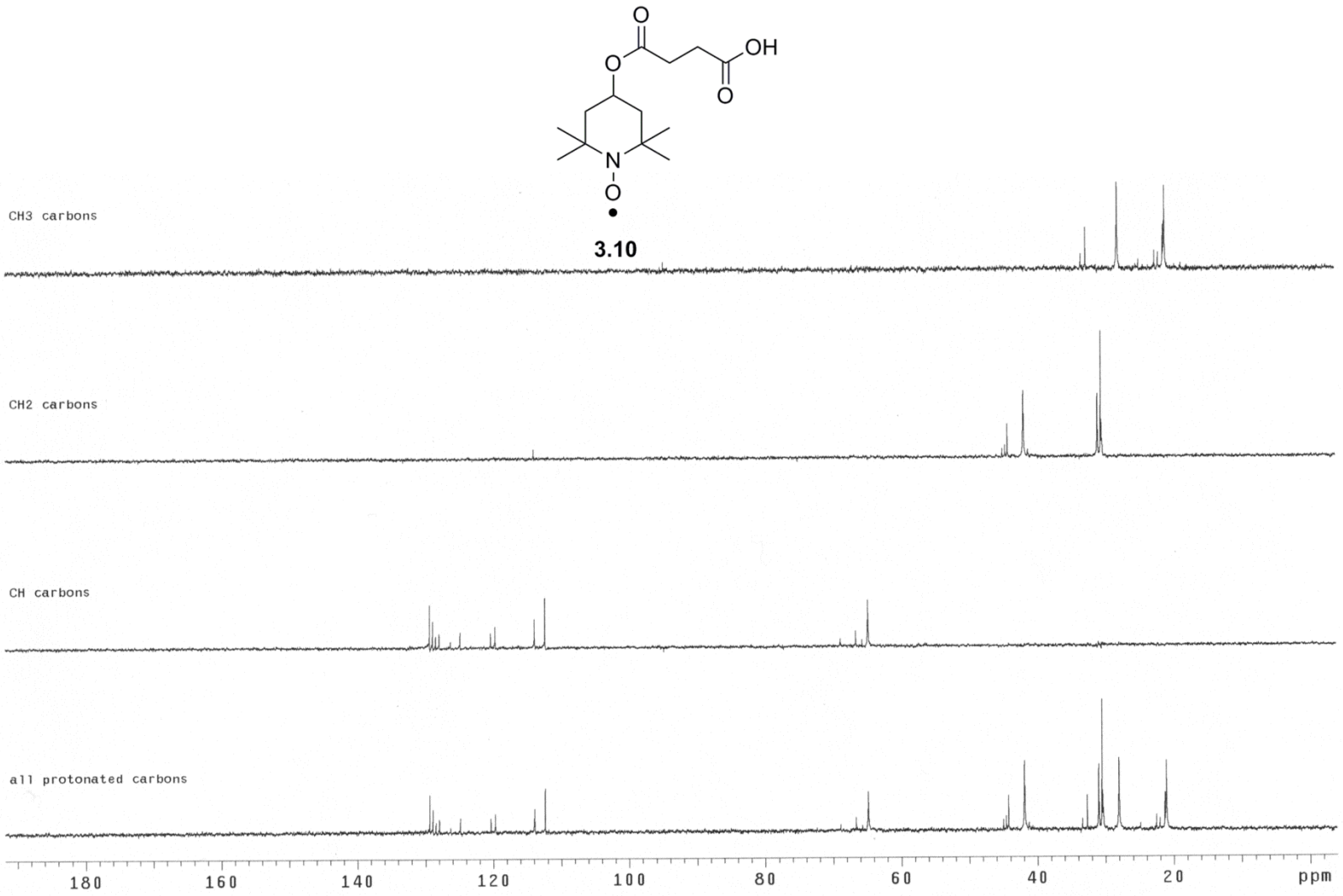
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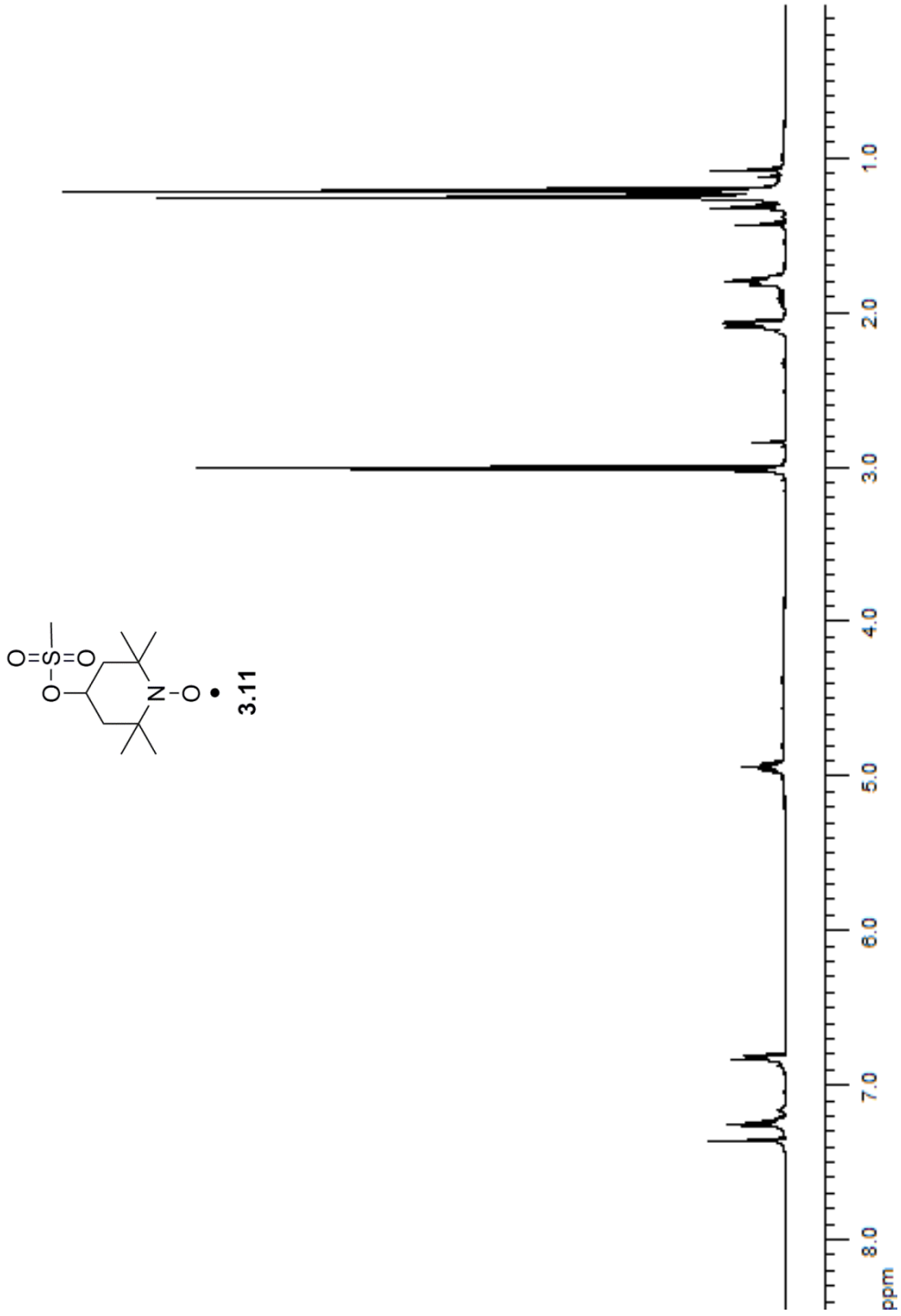
3.10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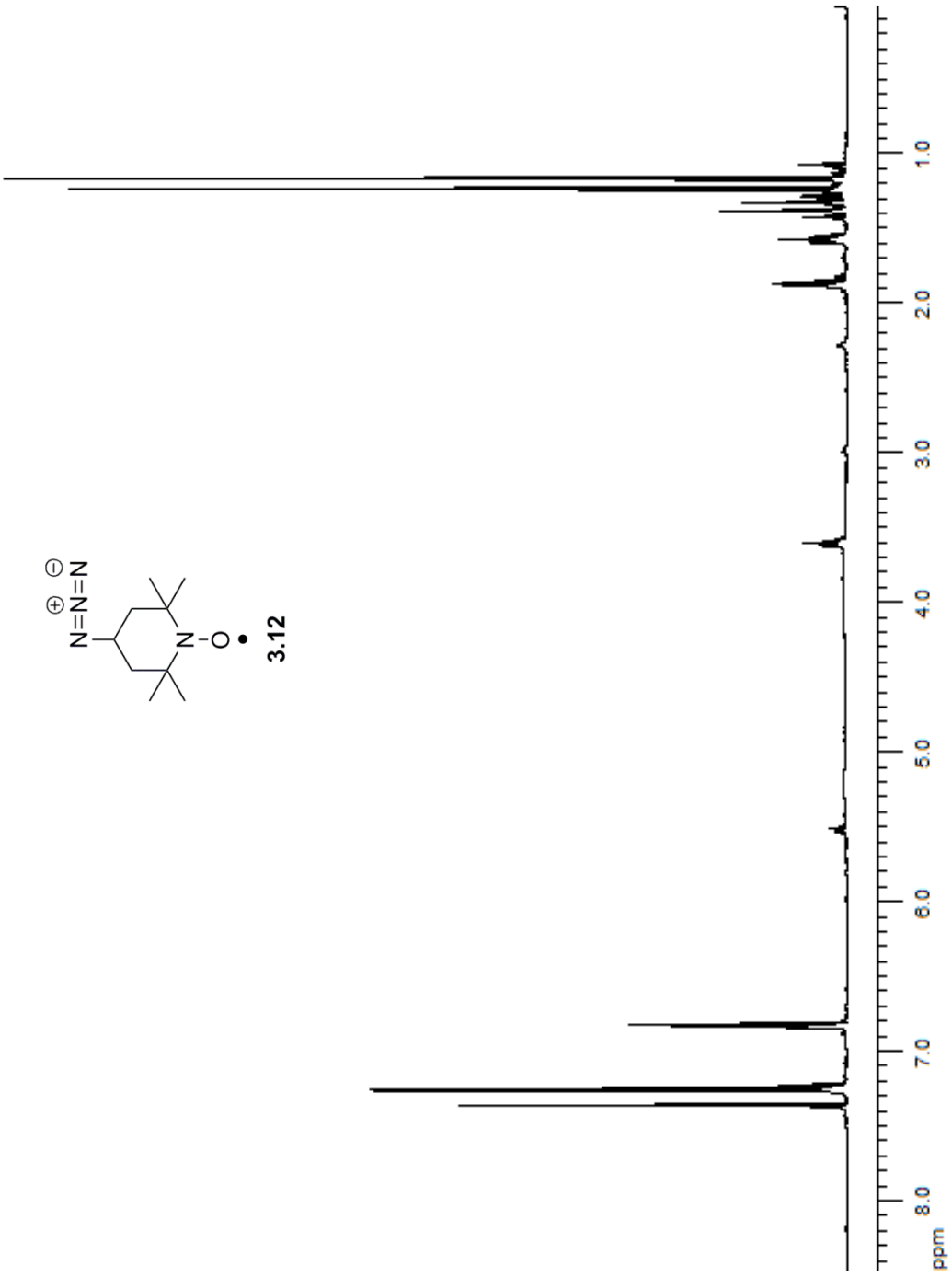
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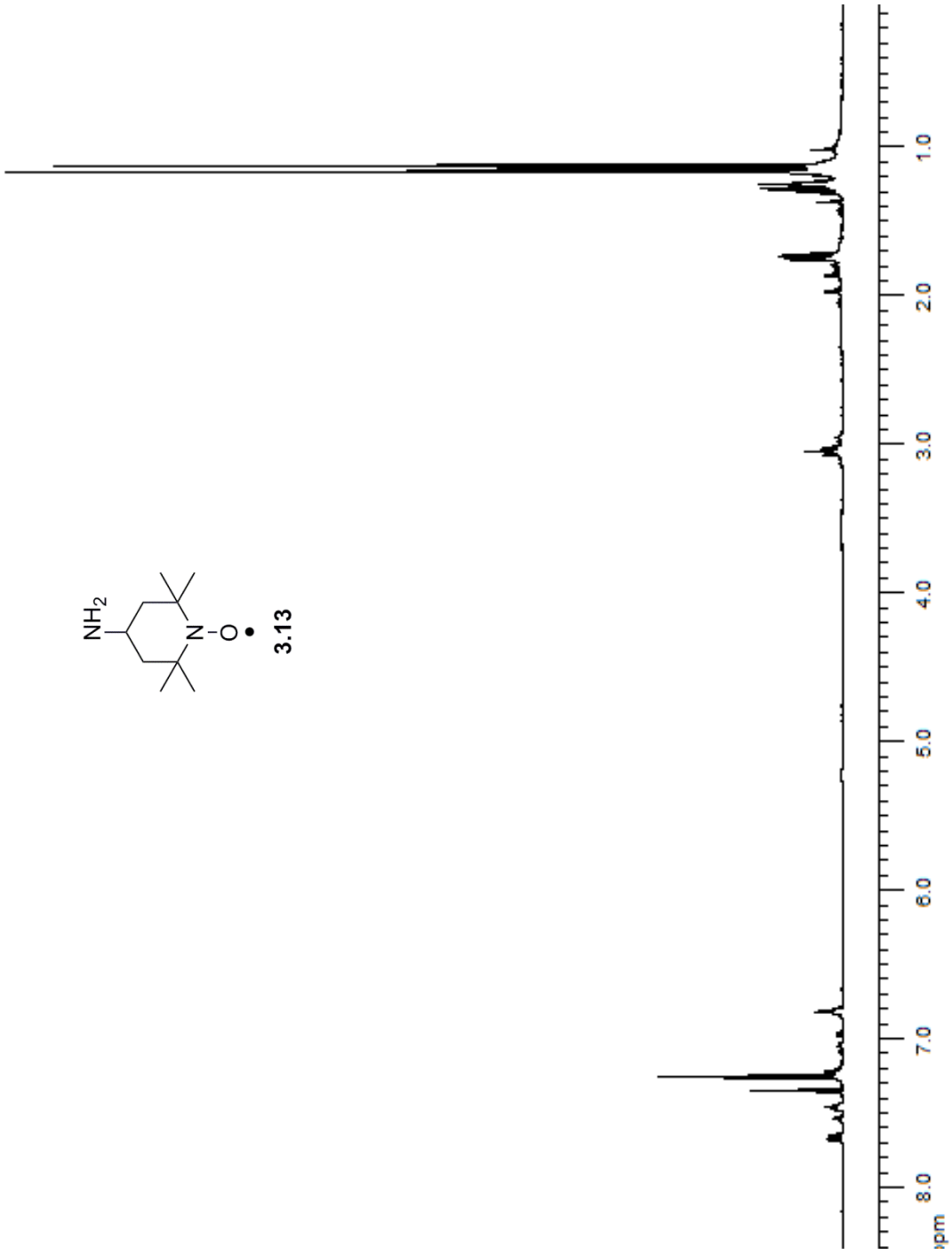
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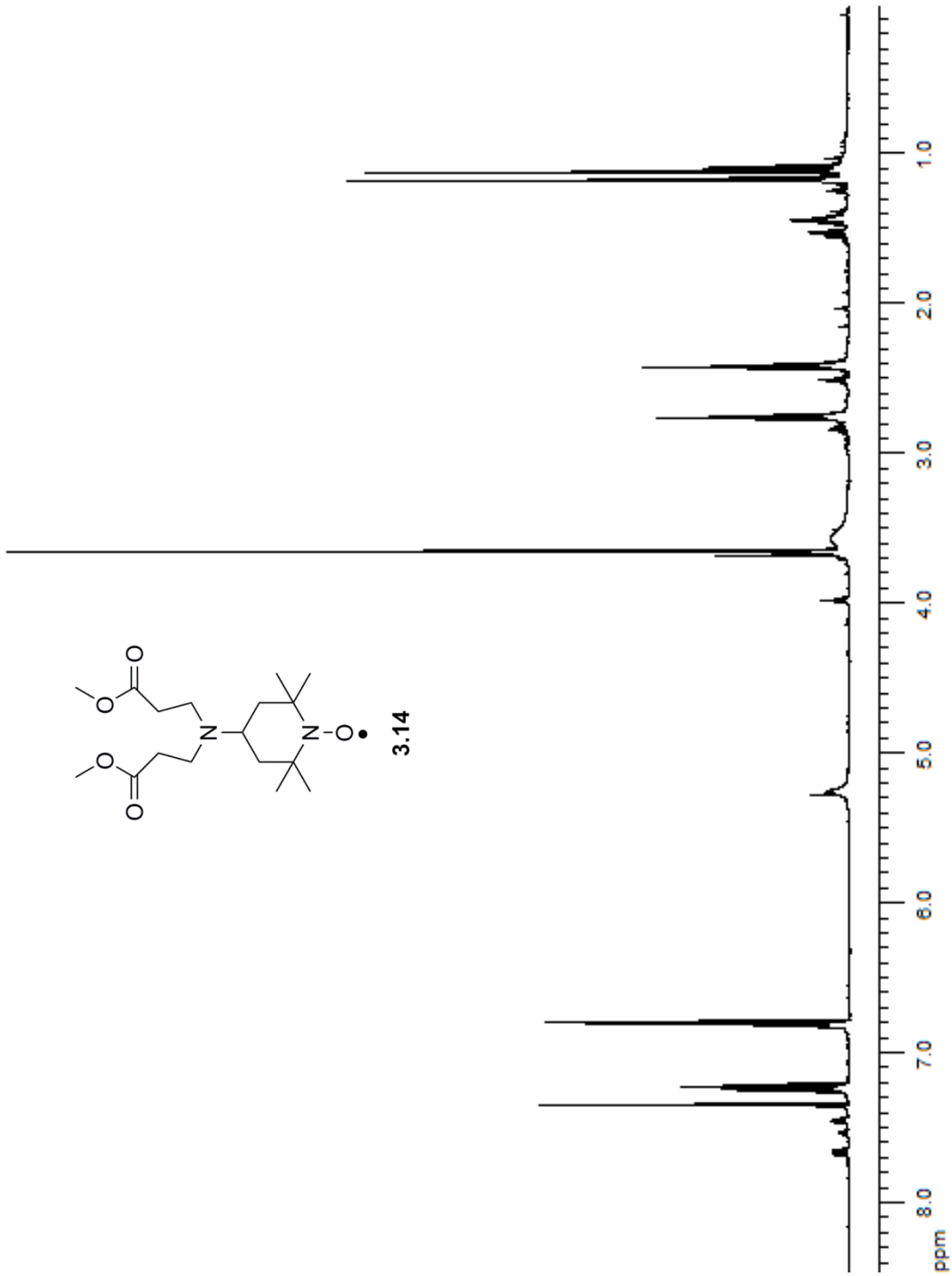
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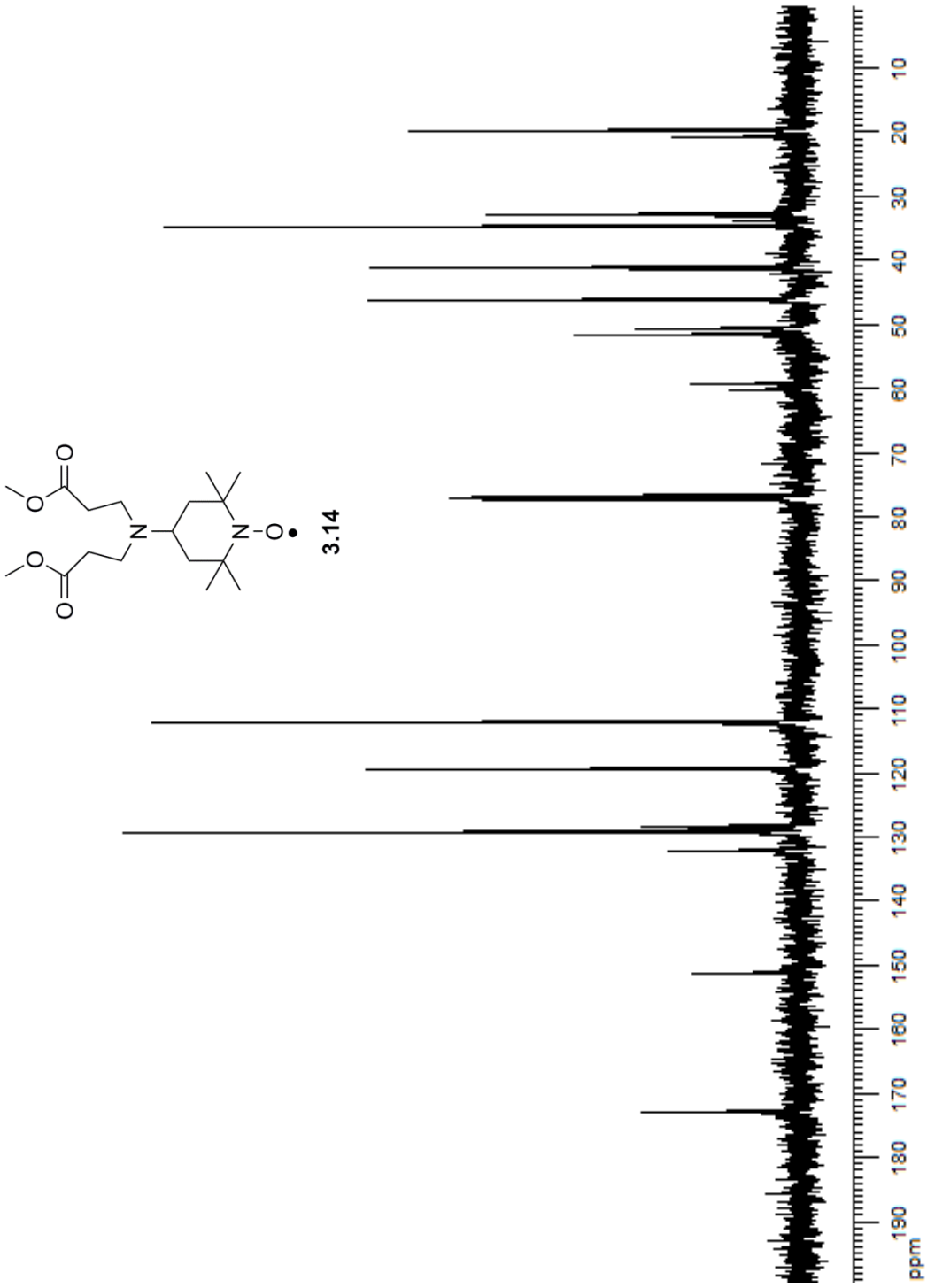
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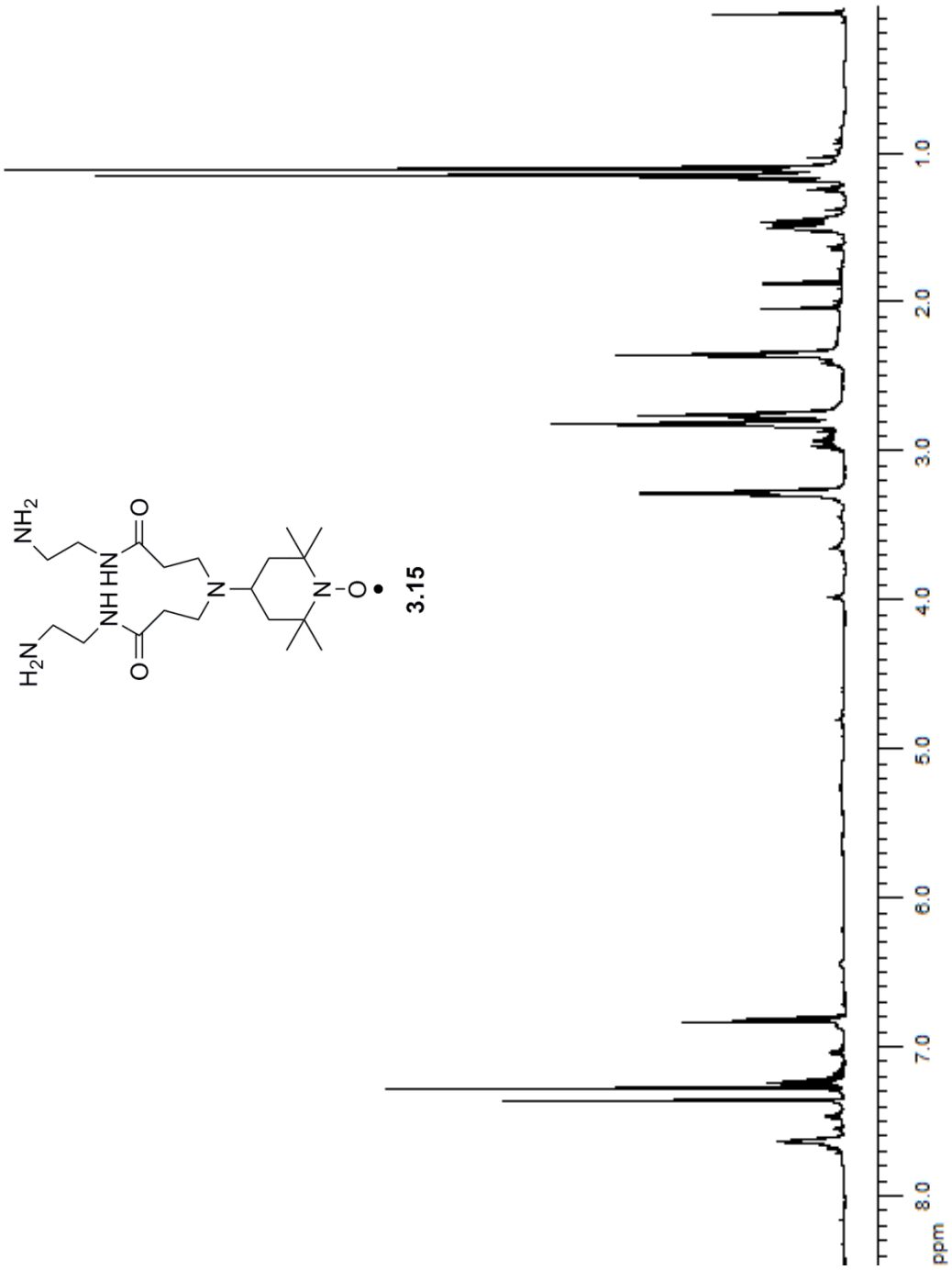
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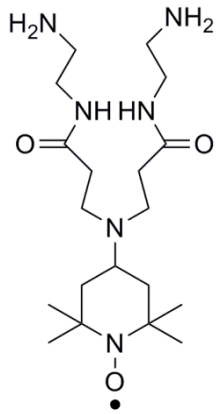
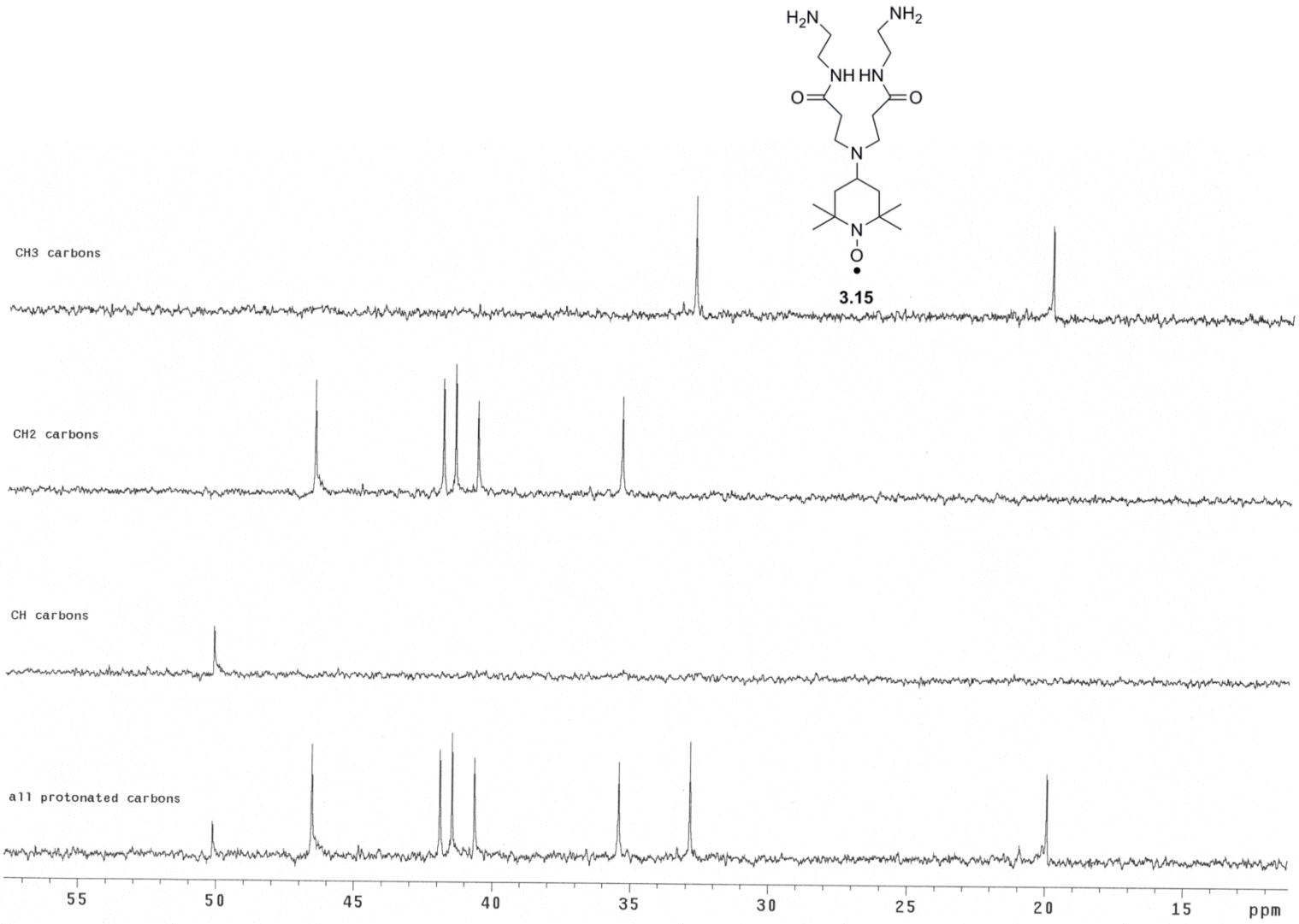
ppm

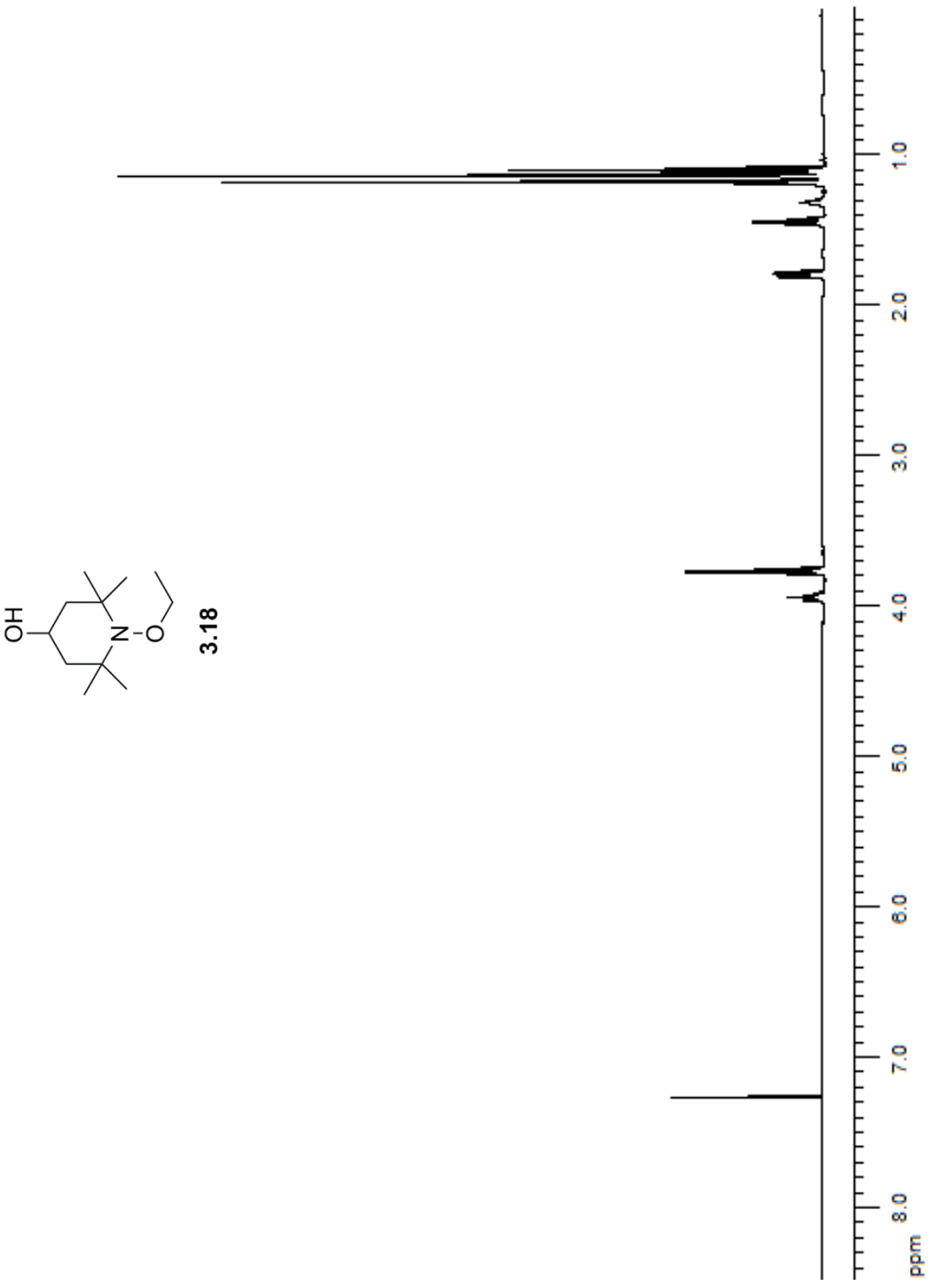

H2N
NH2
NH HN
O
O
N
N
O

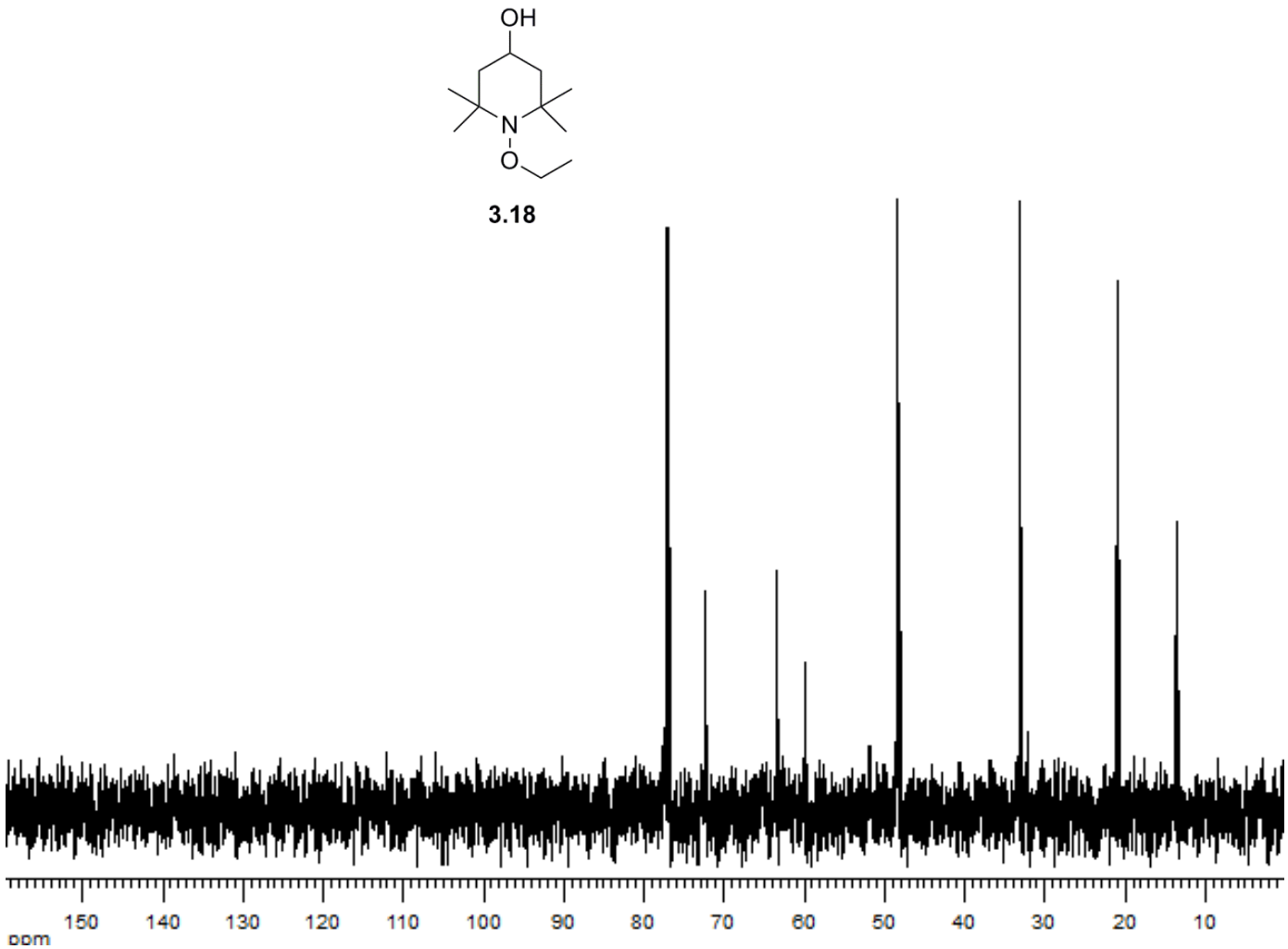
3.15

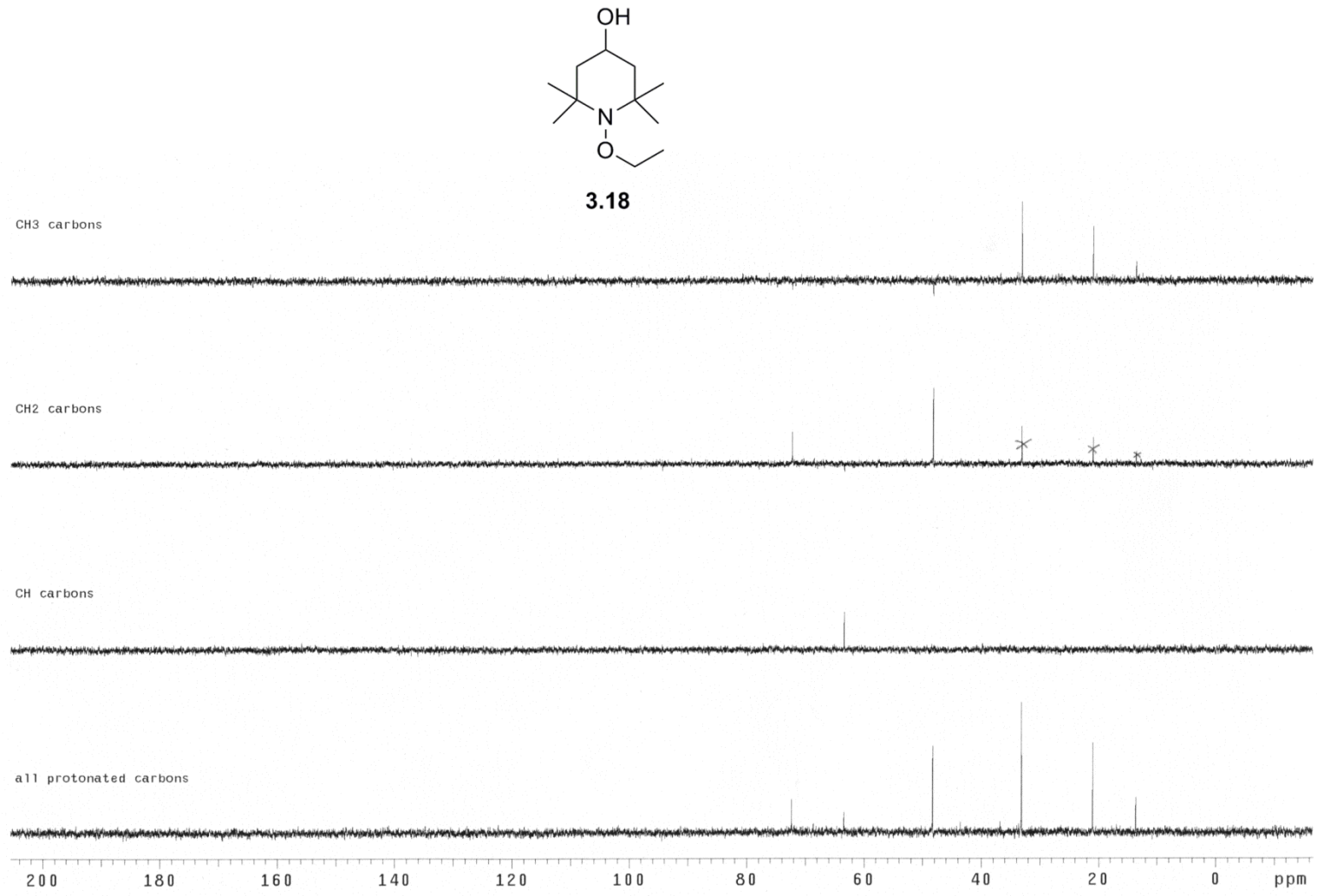
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

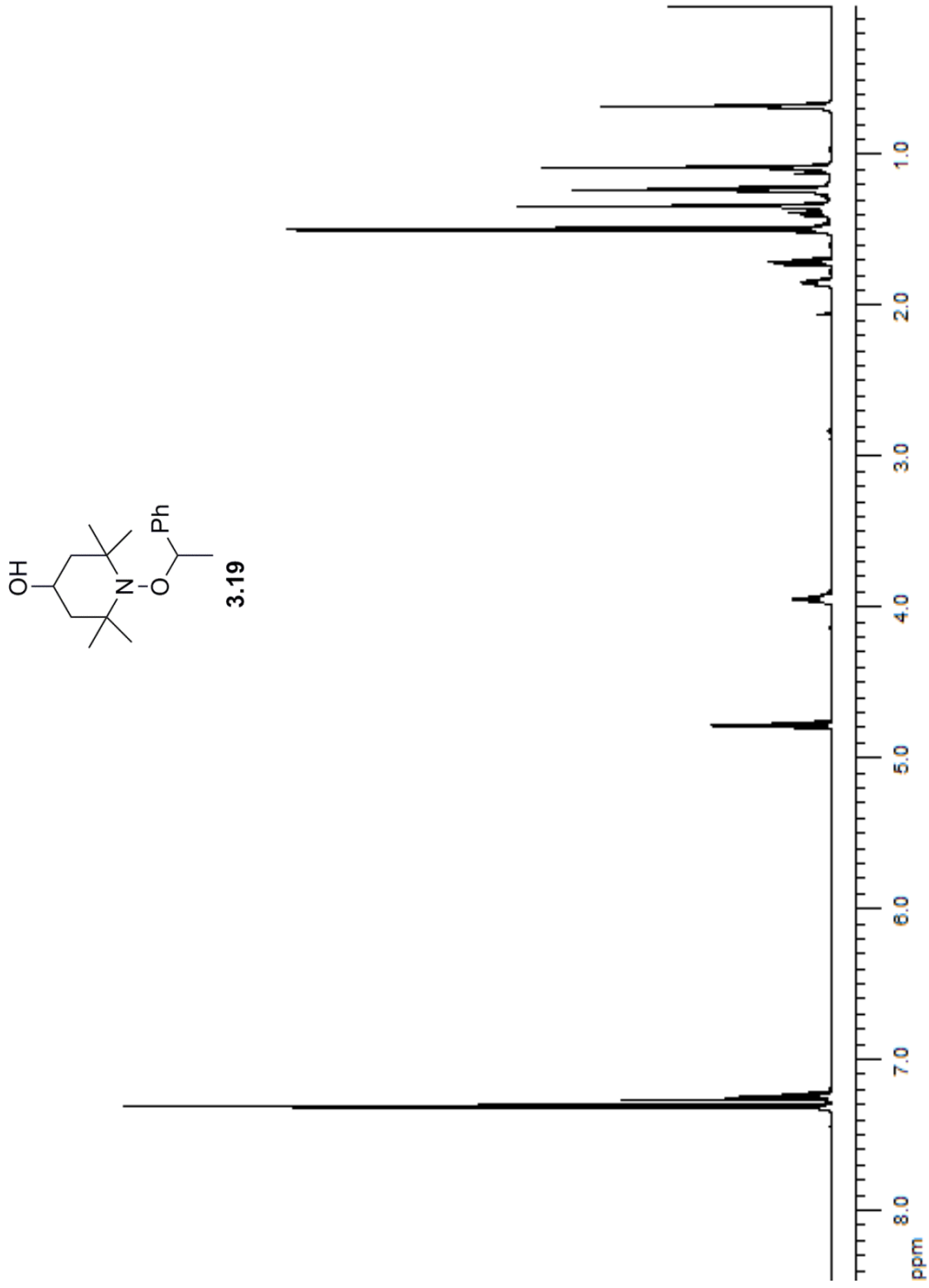

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
55
50
45
40
35
30
25
20
15
ppm

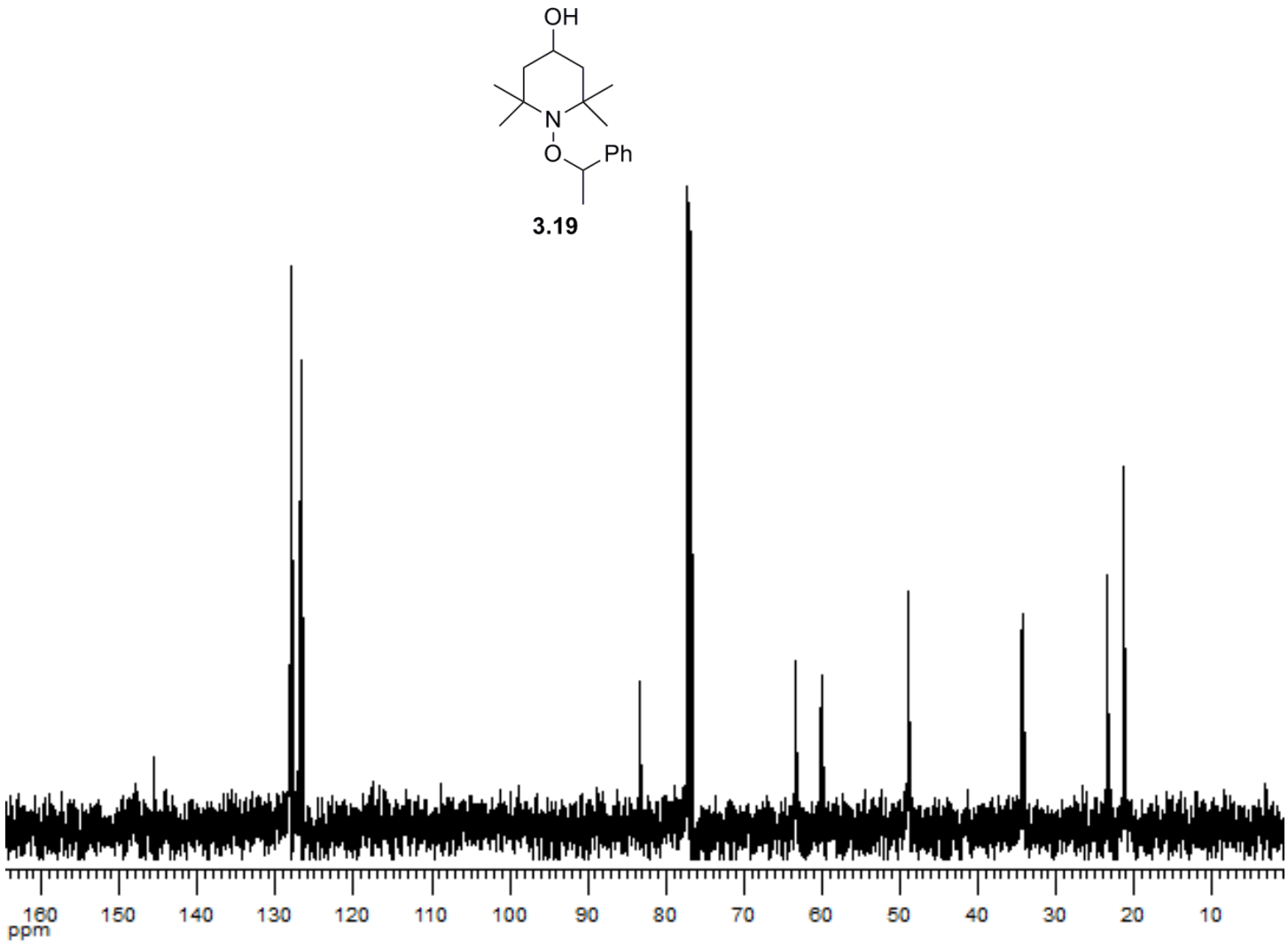
3.15

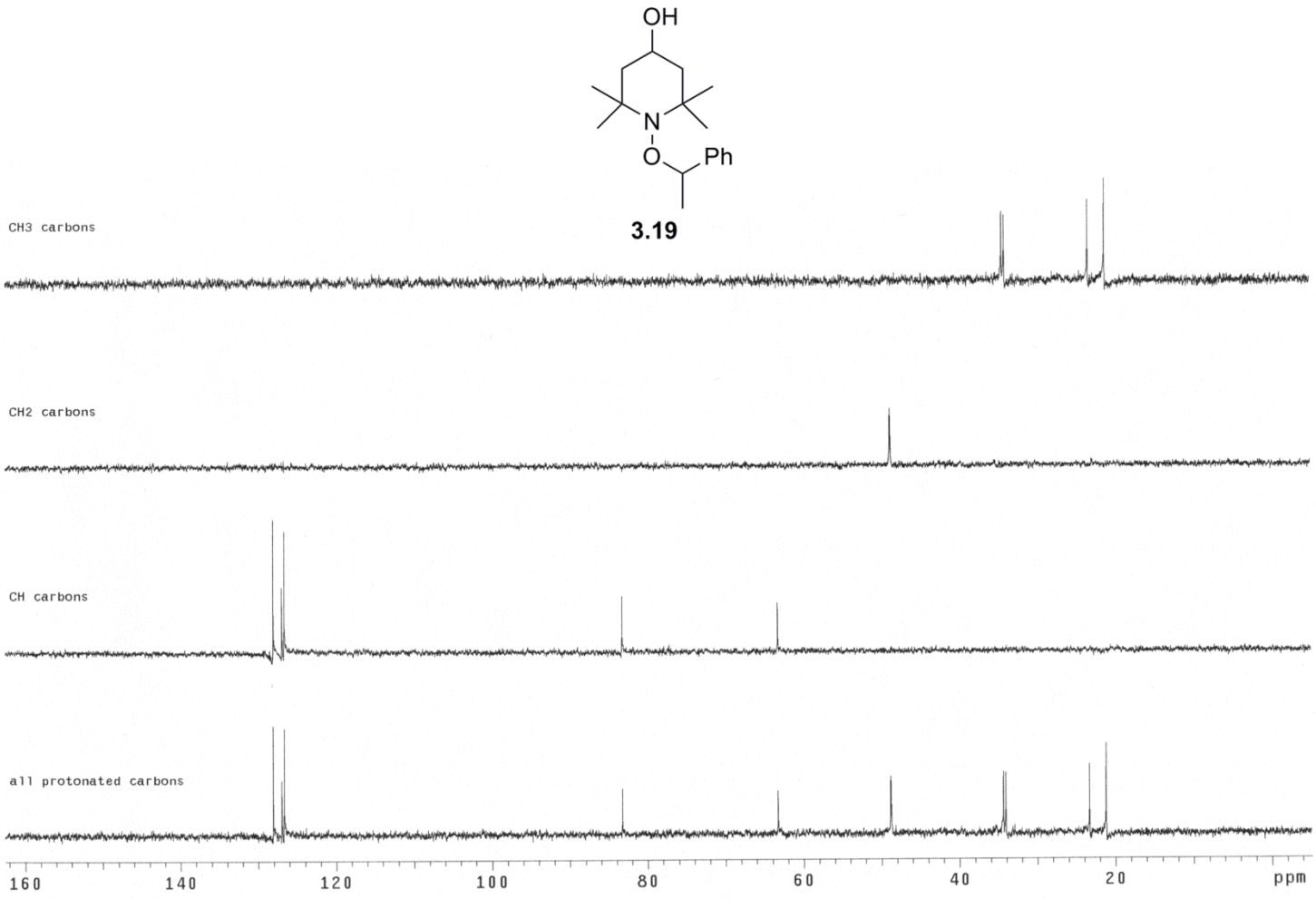

OH
N
O
3.18
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

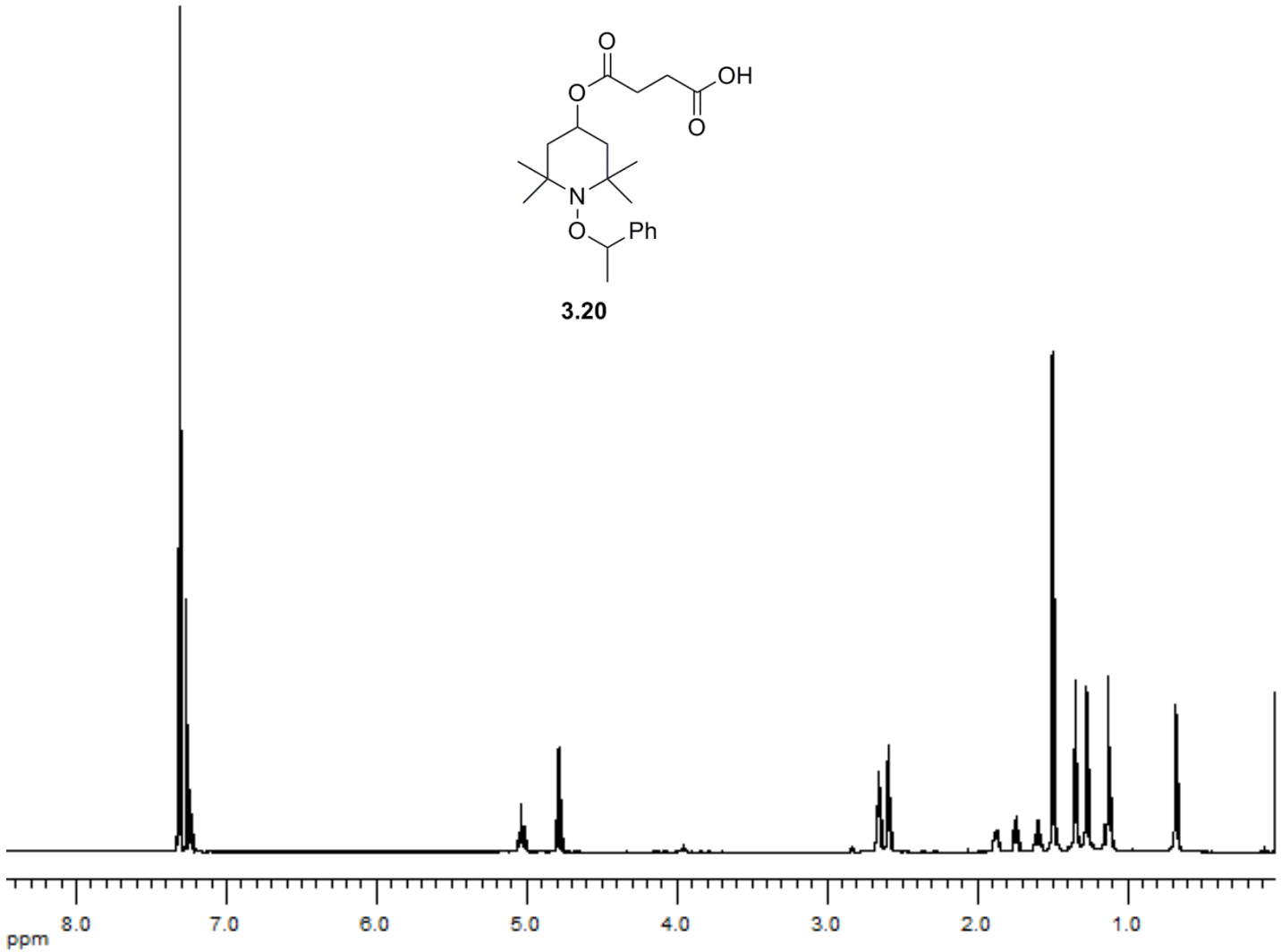

OH
N
O
3.18
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
N
O
3.18
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

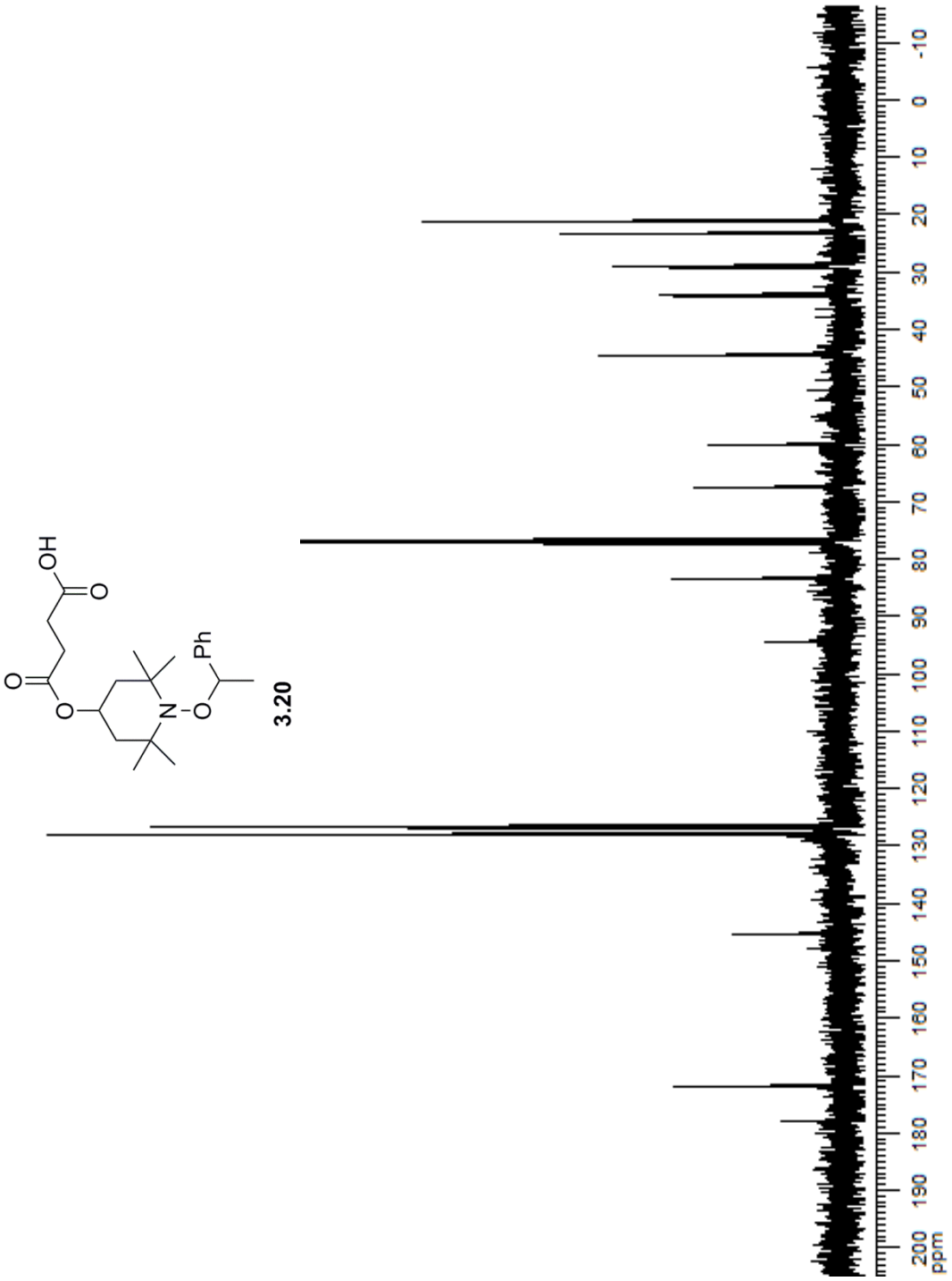

OH
N
O
Ph
3.19
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

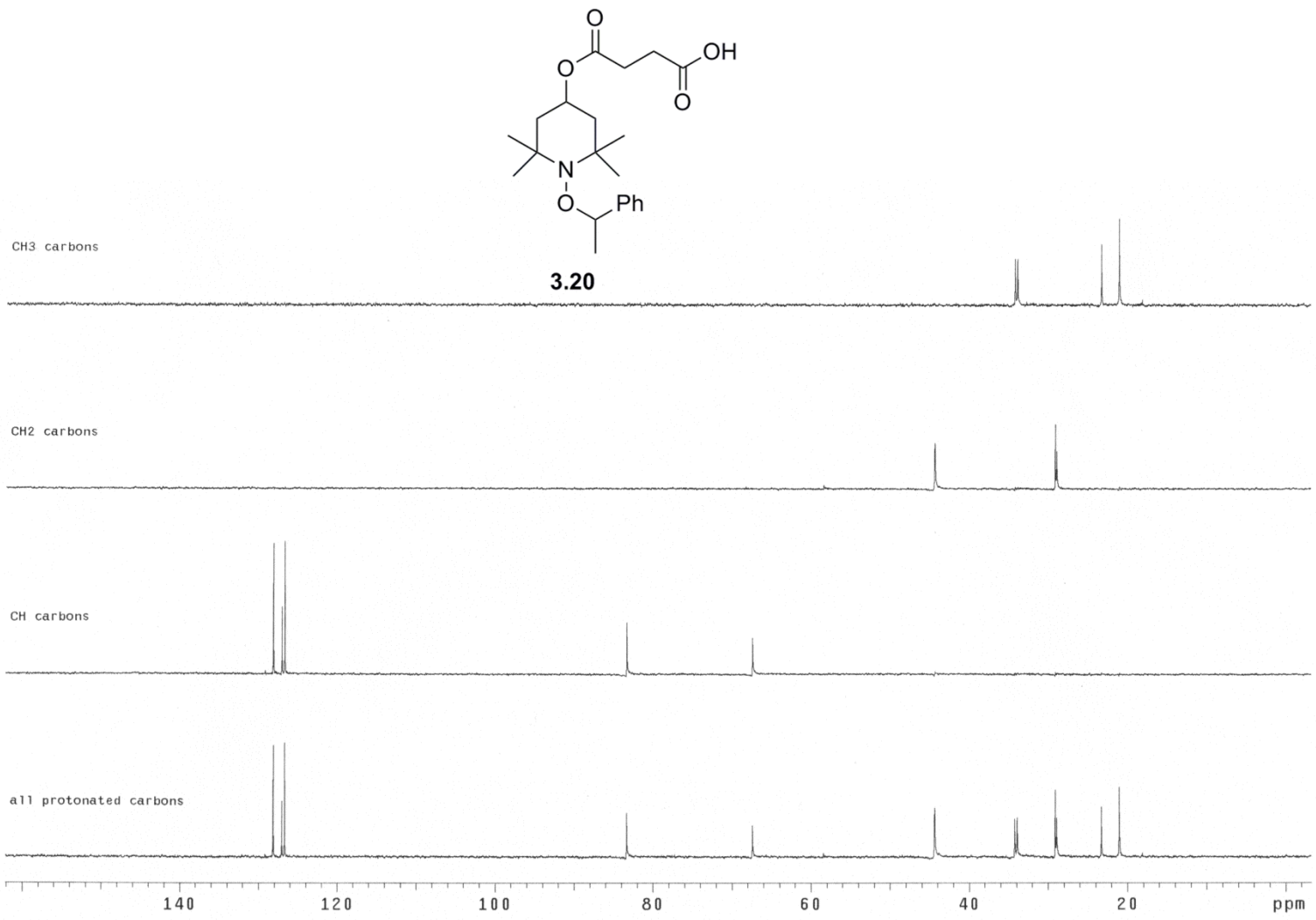

OH
N
O
Ph
3.19
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
N
O
Ph
3.19
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm

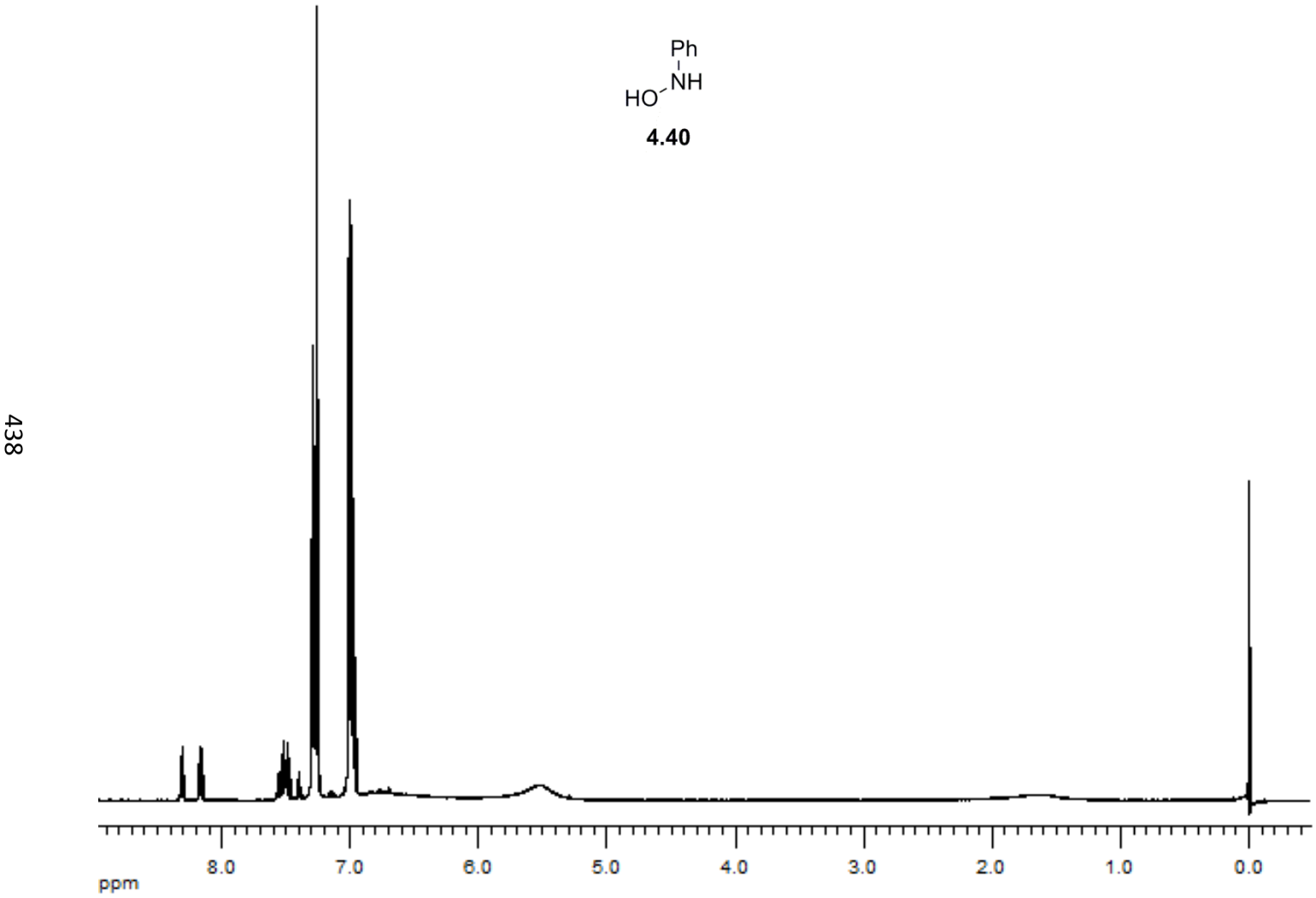


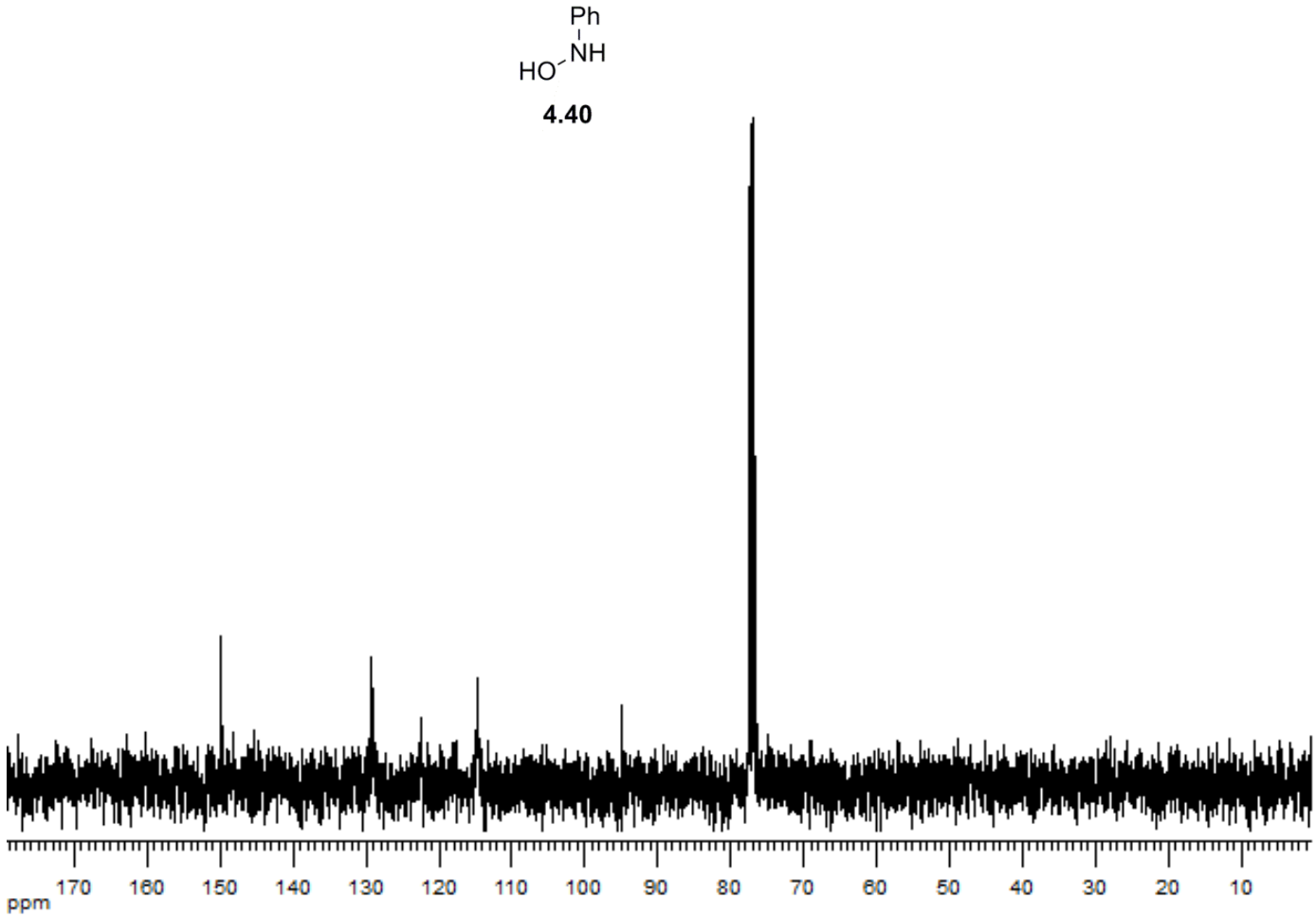
3.20


OH
O
O
O
O
N
O
Ph
3.20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

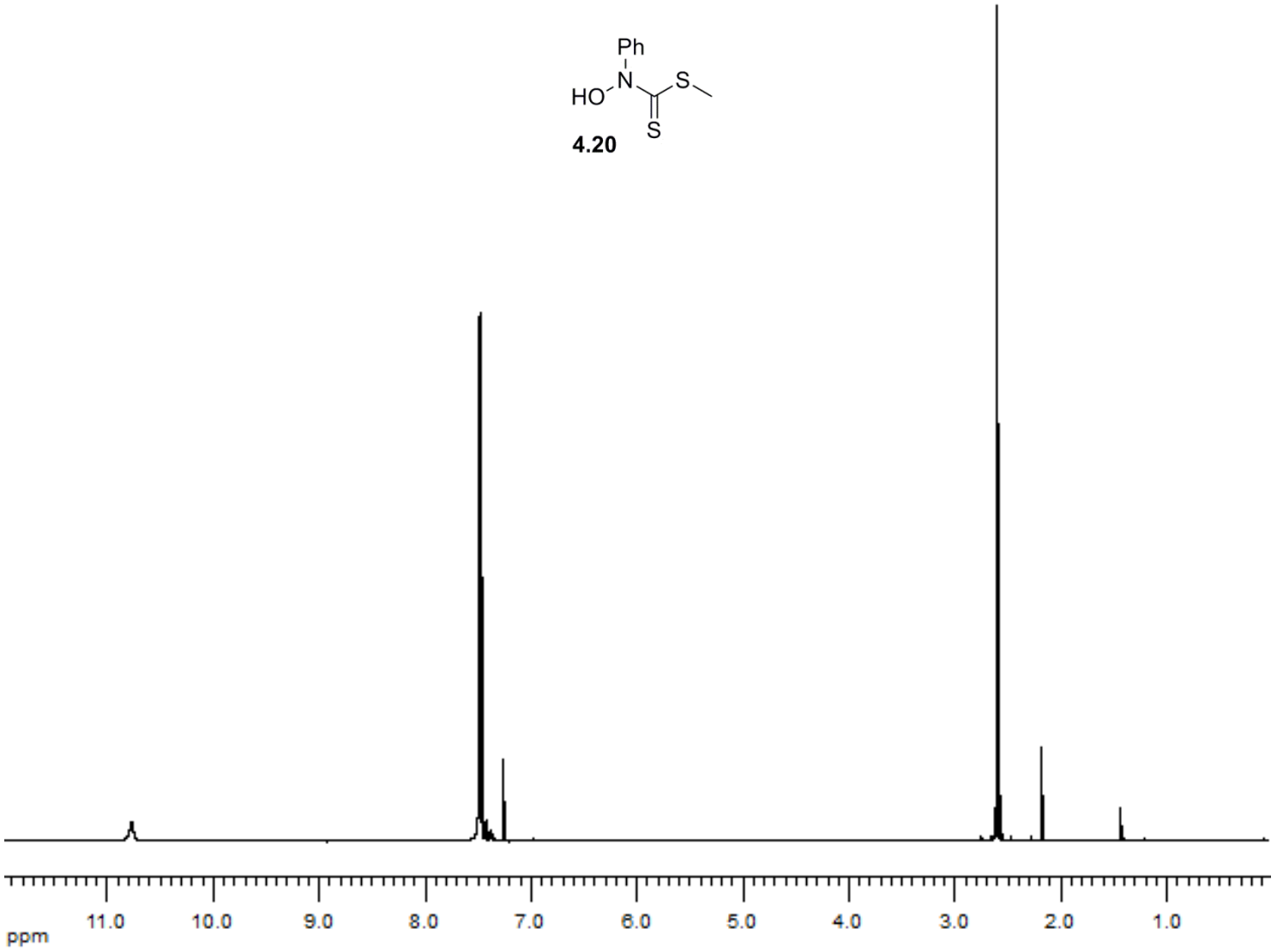

O
OH
O
O
N
O
Ph
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
140
120
100
80
60
40
20
ppm

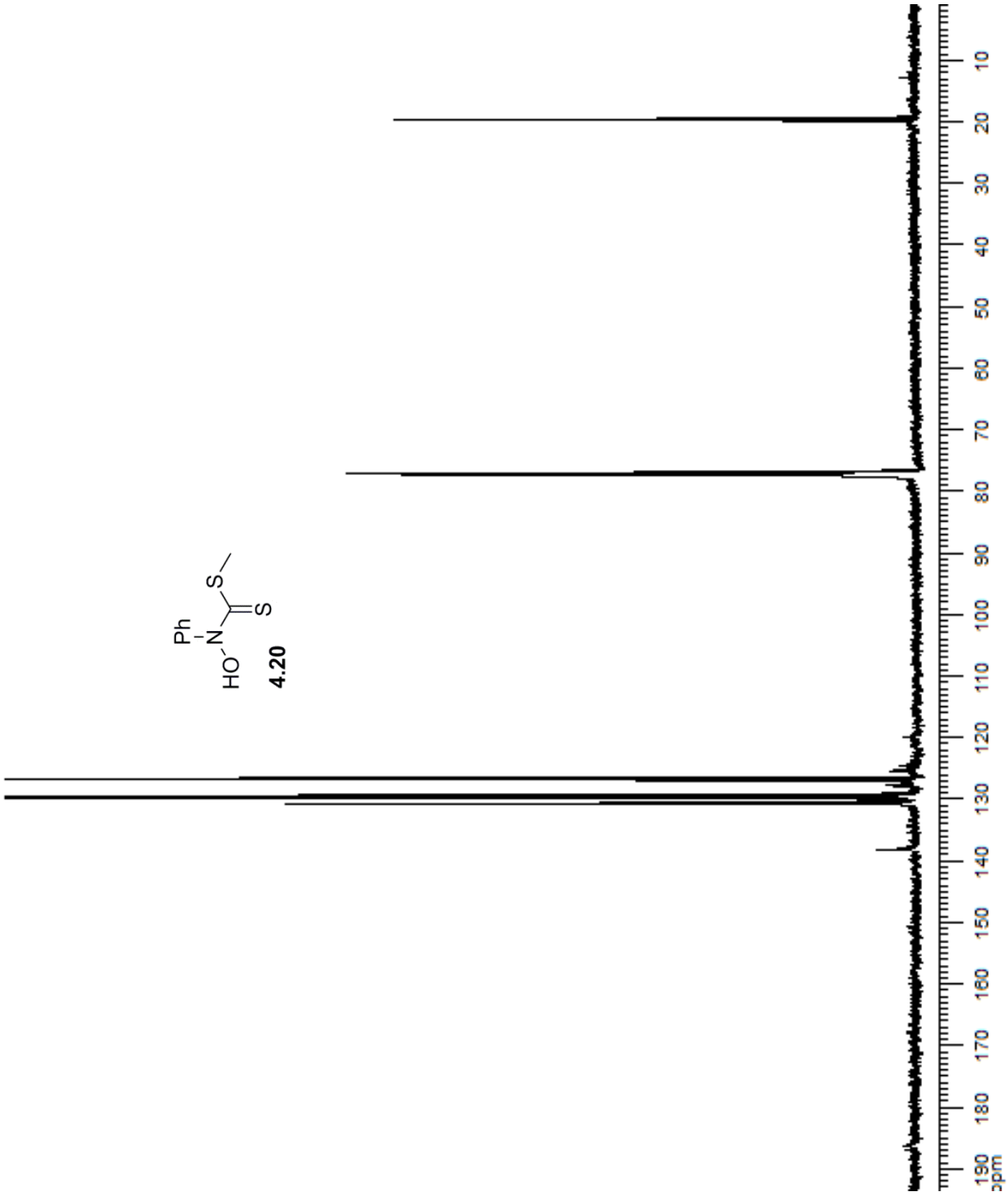
3.20

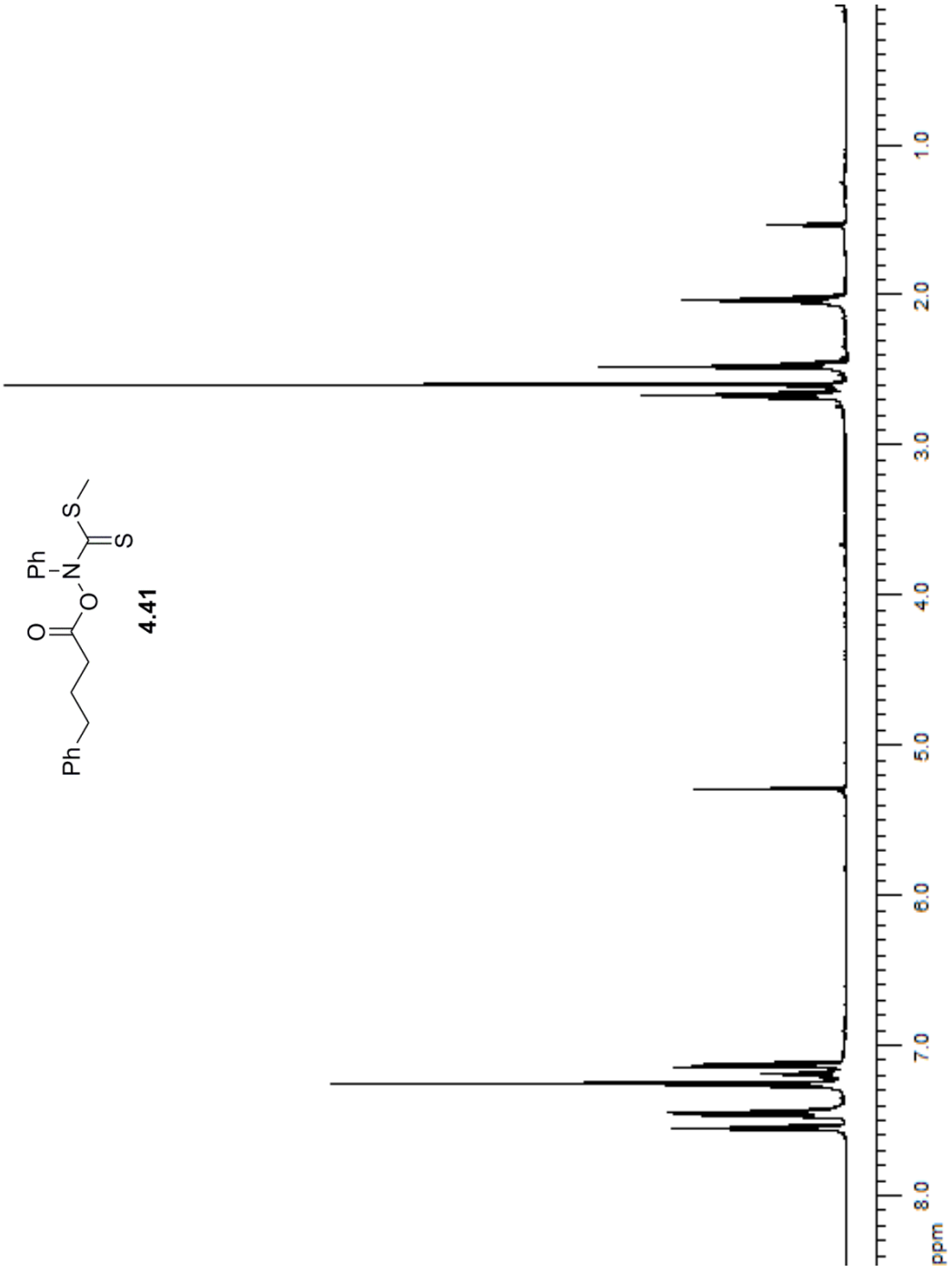

Ph
NH
HO
4.40
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

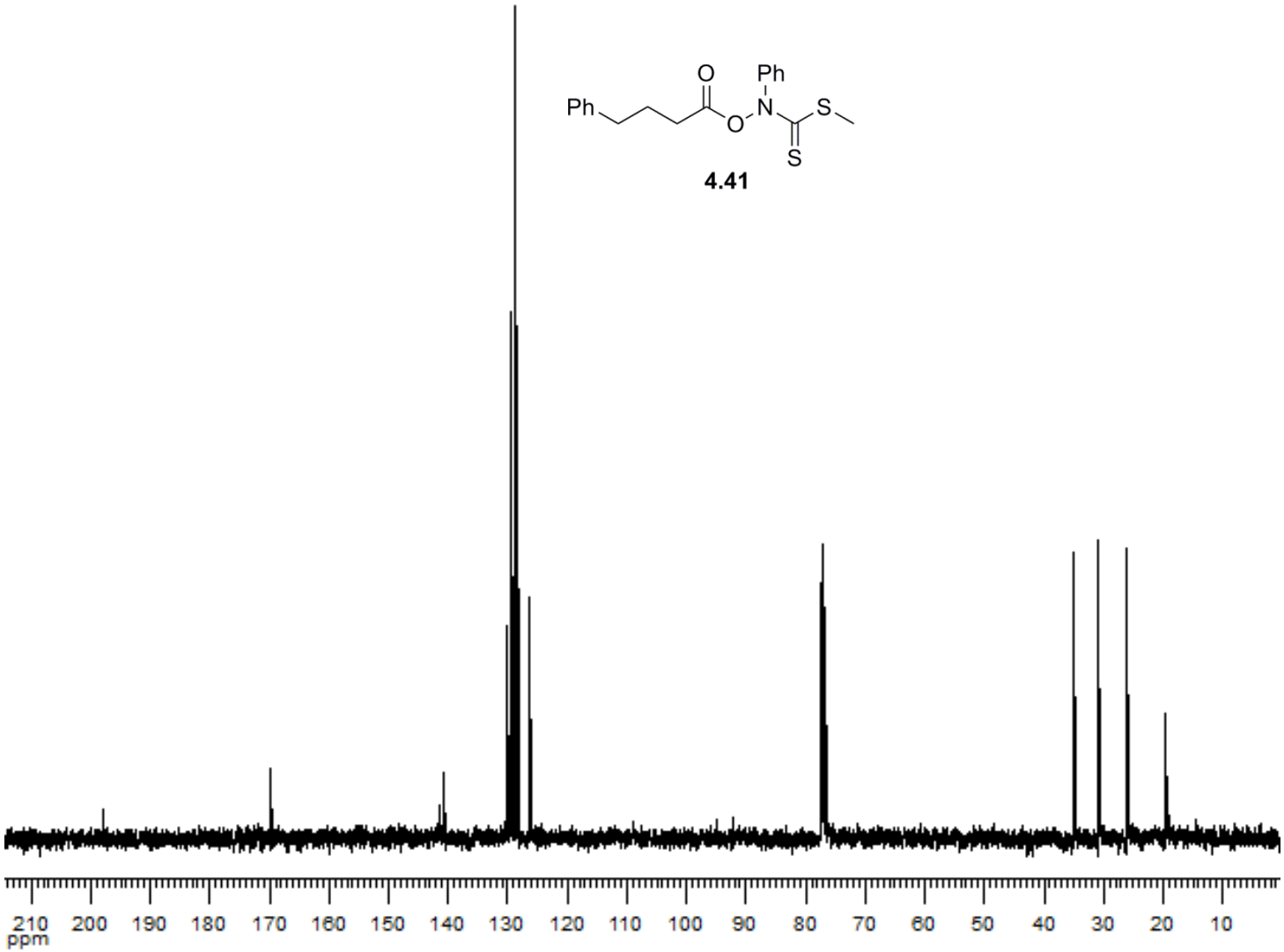

Ph
NH
HO
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

4.40

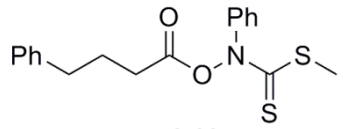

Ph
N
HO
S
S
4.20
ppm
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


Ph
N
HO
S
S
4.20
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm

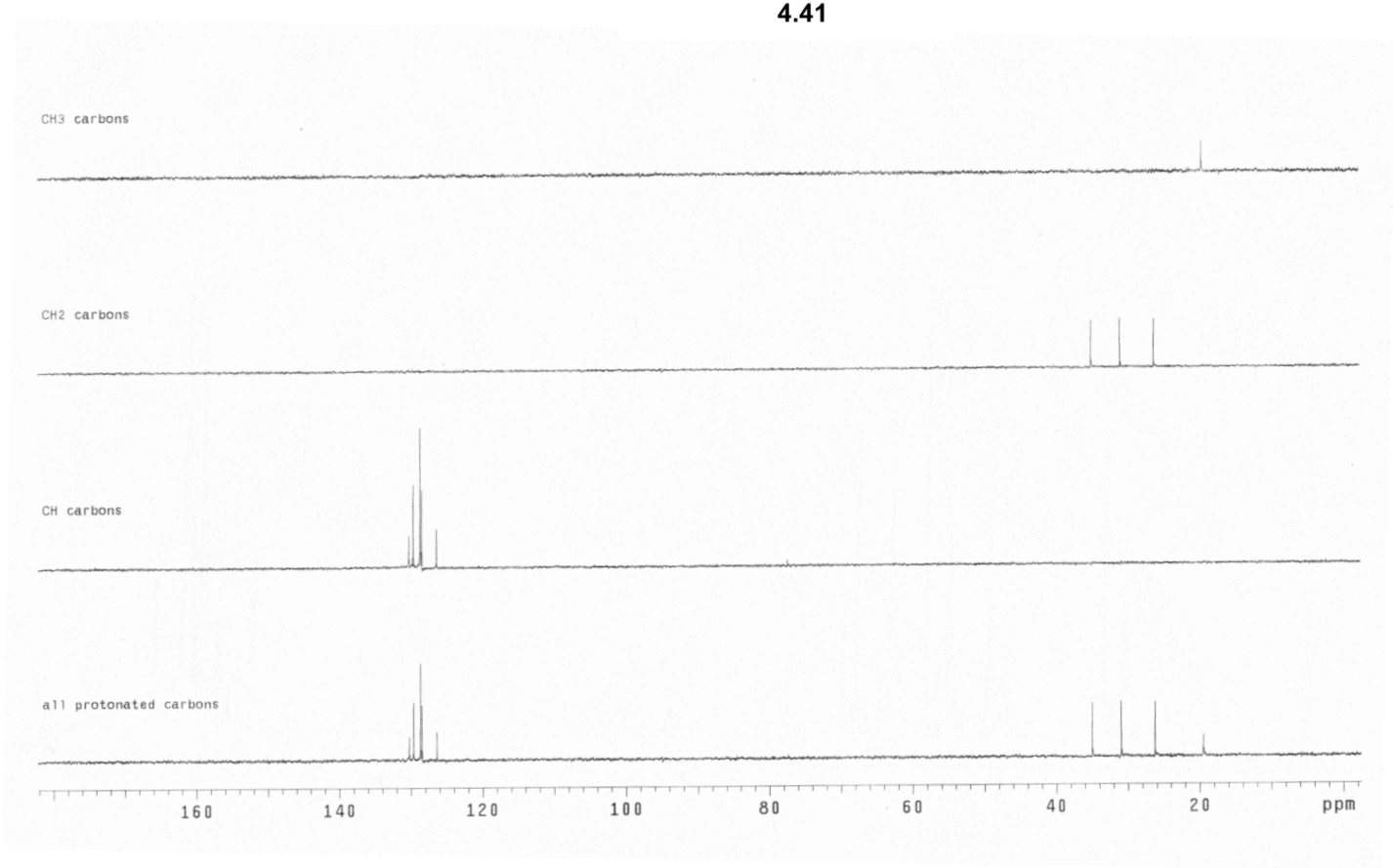

Ph
N
O
O
S
S
Ph
4.41
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

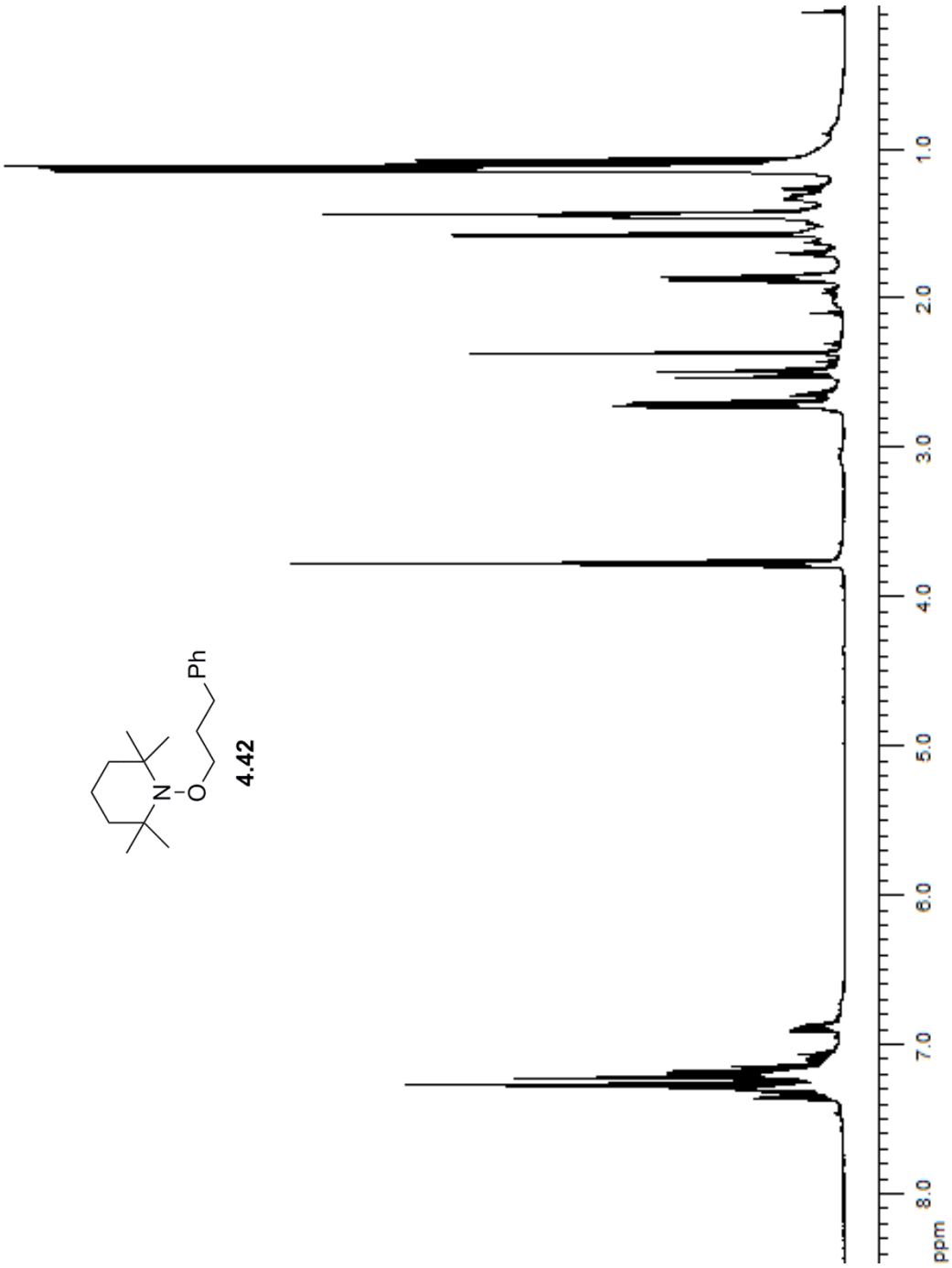

O
Ph
Ph
N
S
O
S
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

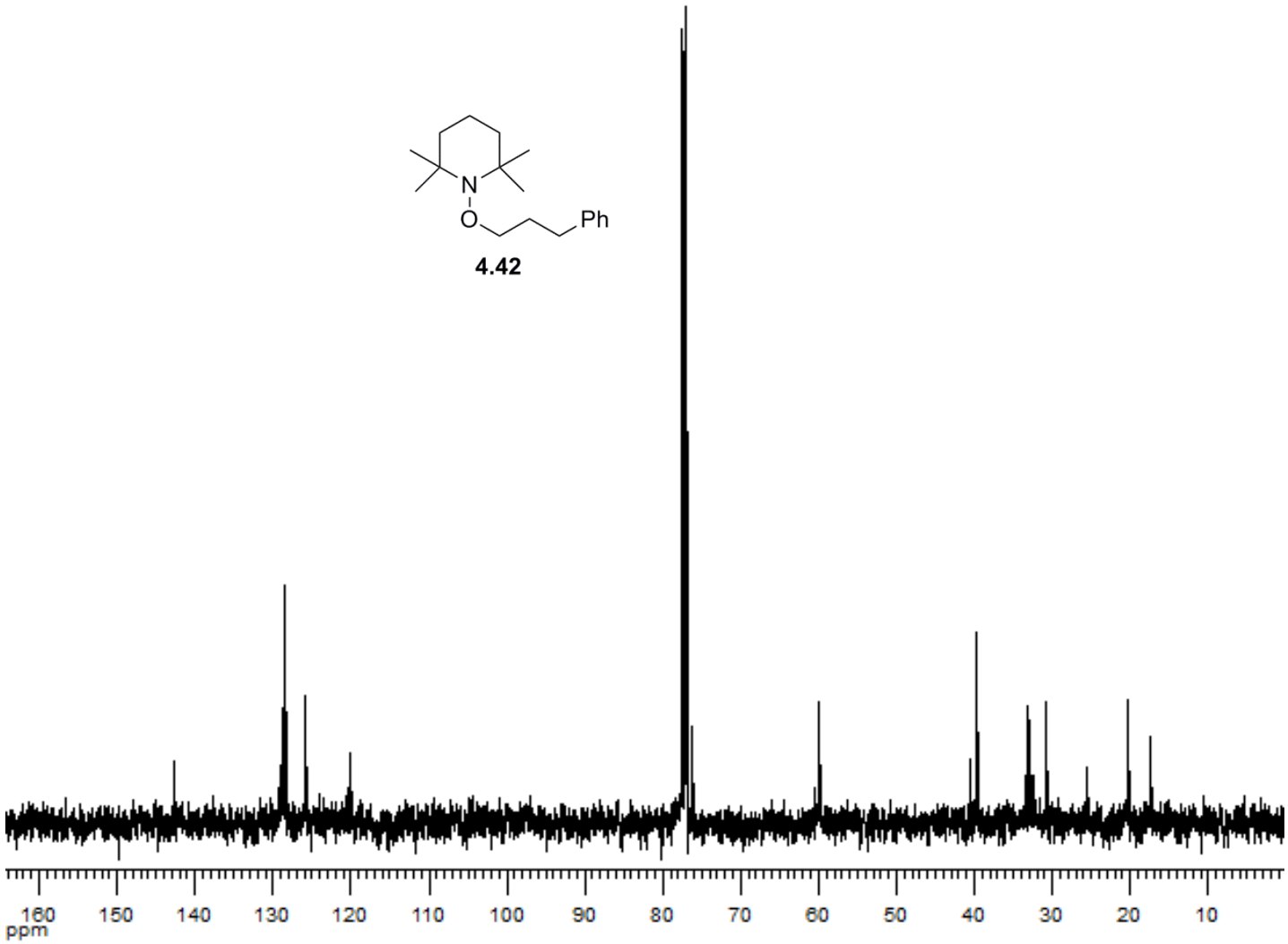
4.41


O
Ph
Ph
N
O
S
S

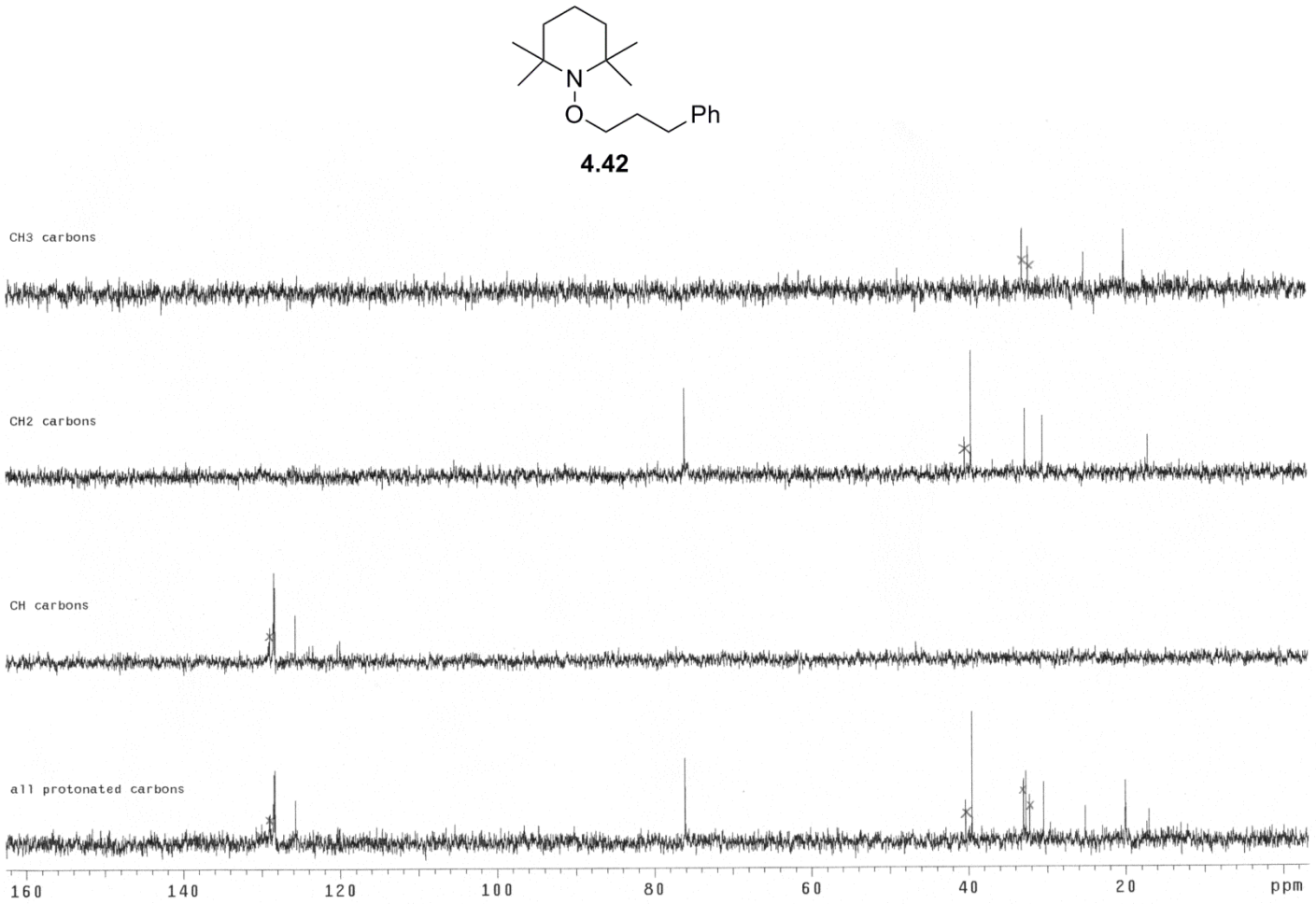
4.41

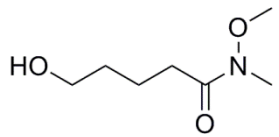

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm


Ph
N
O
4.42
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

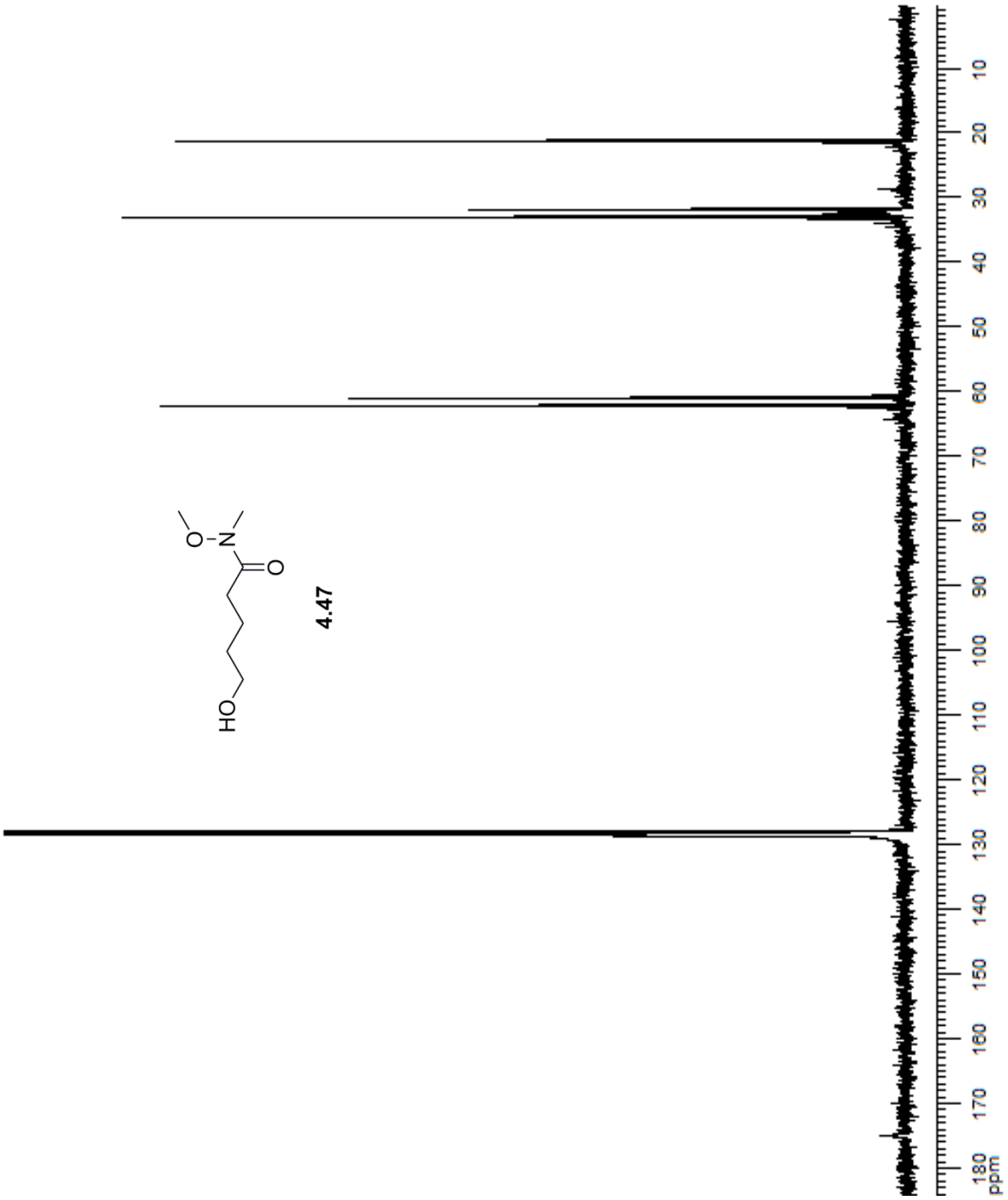


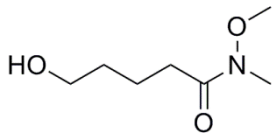
4.42


N
O
Ph
4.42
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm

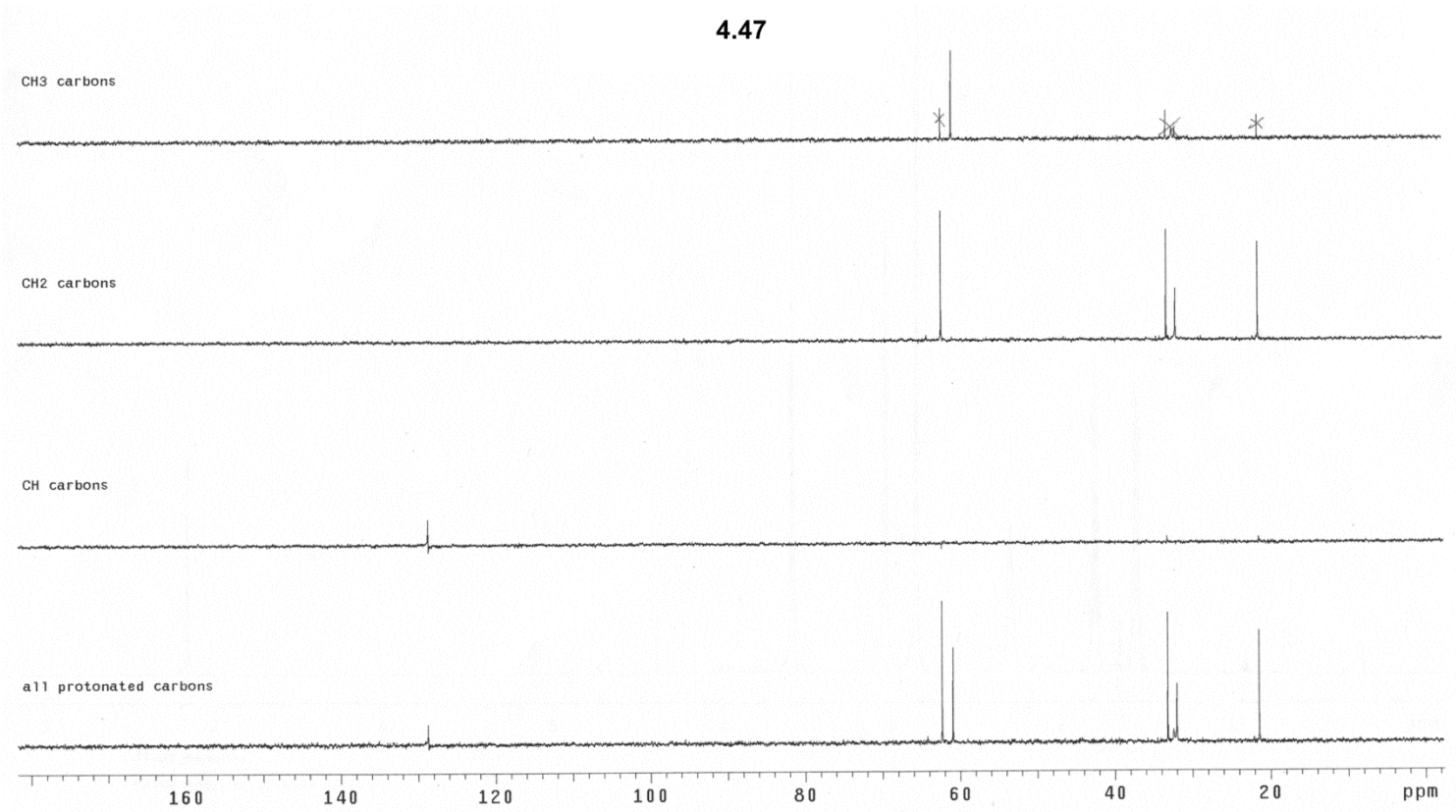


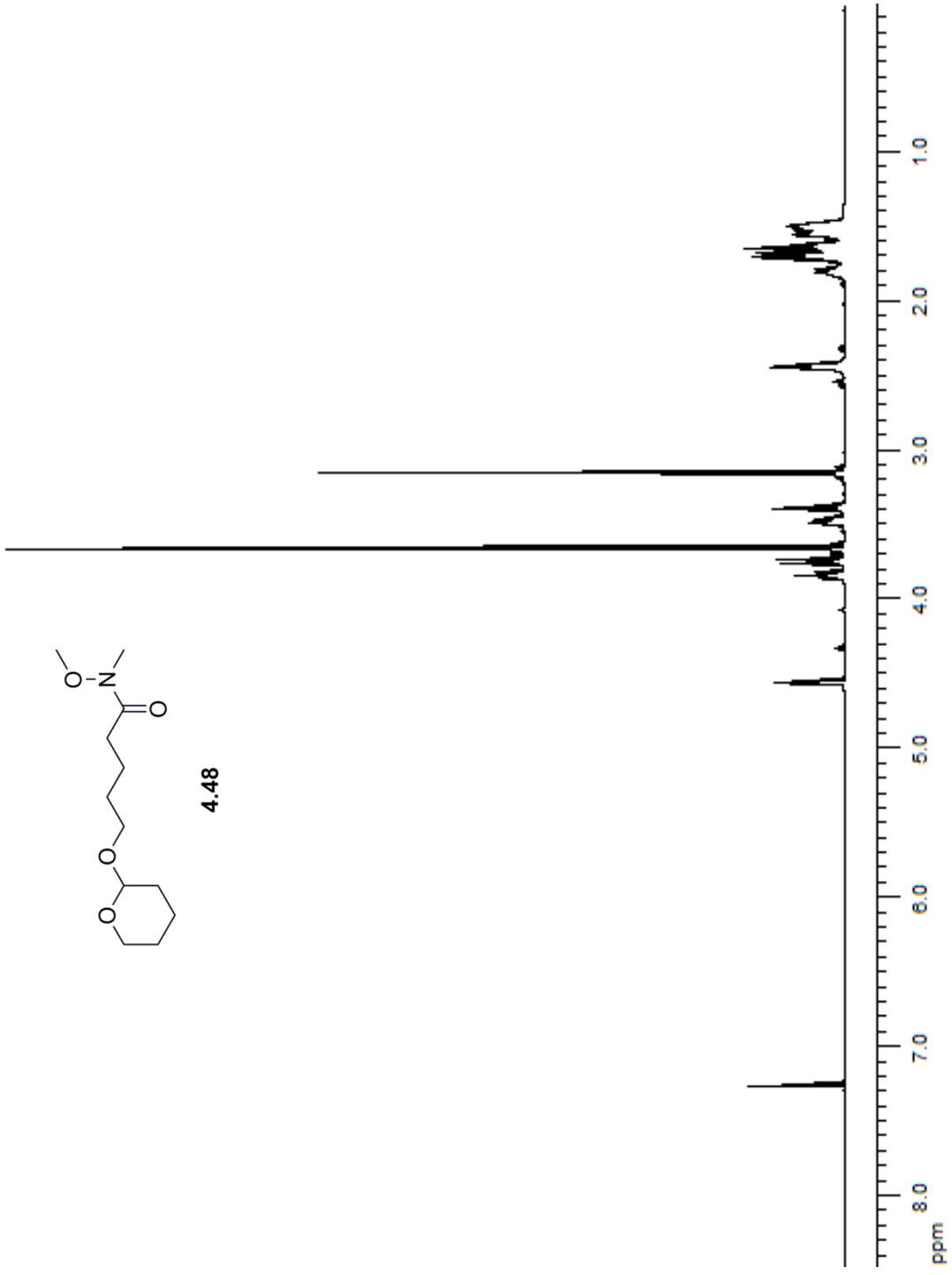
4.47

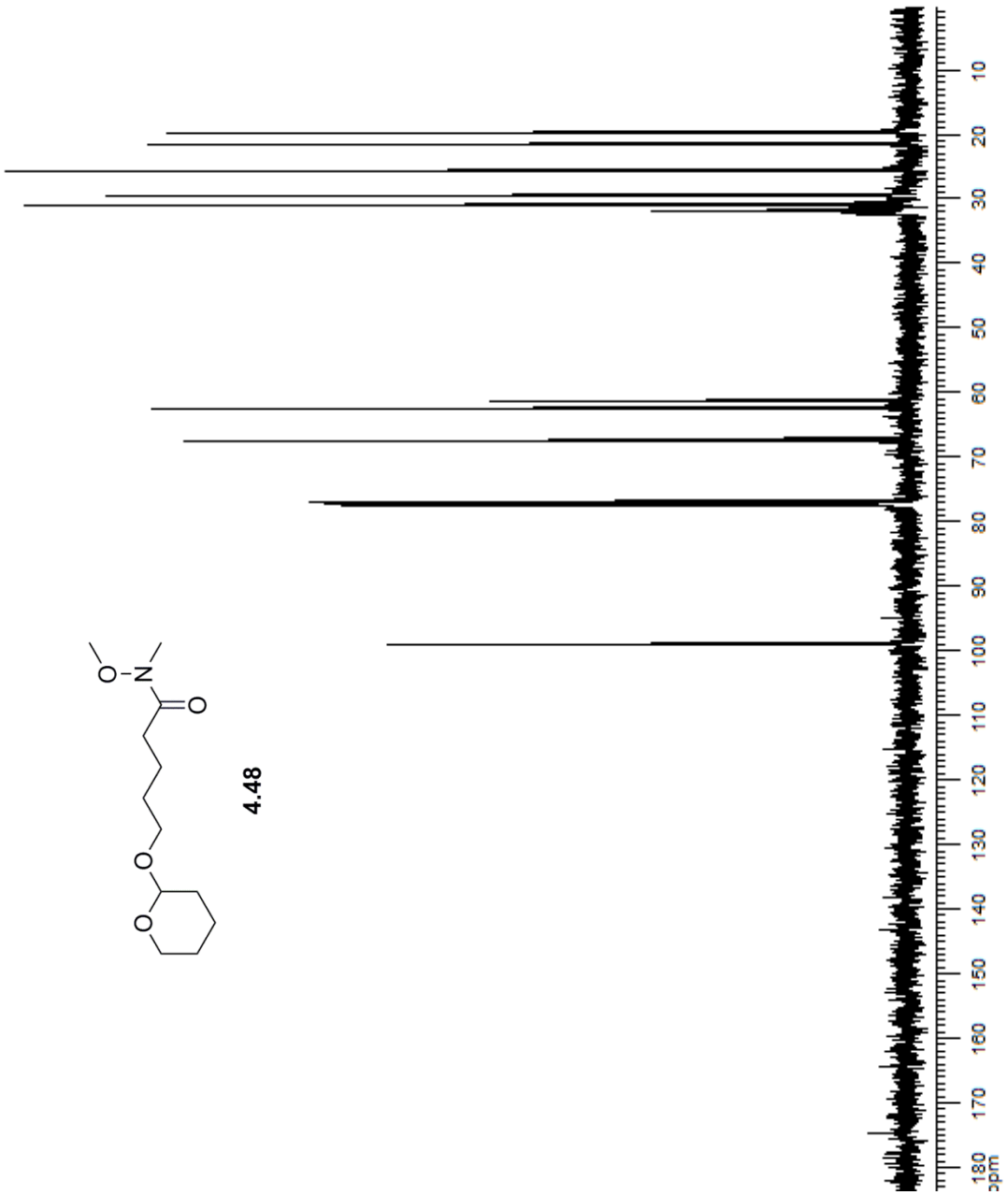

O
N
O
HO
4.47
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
ppm

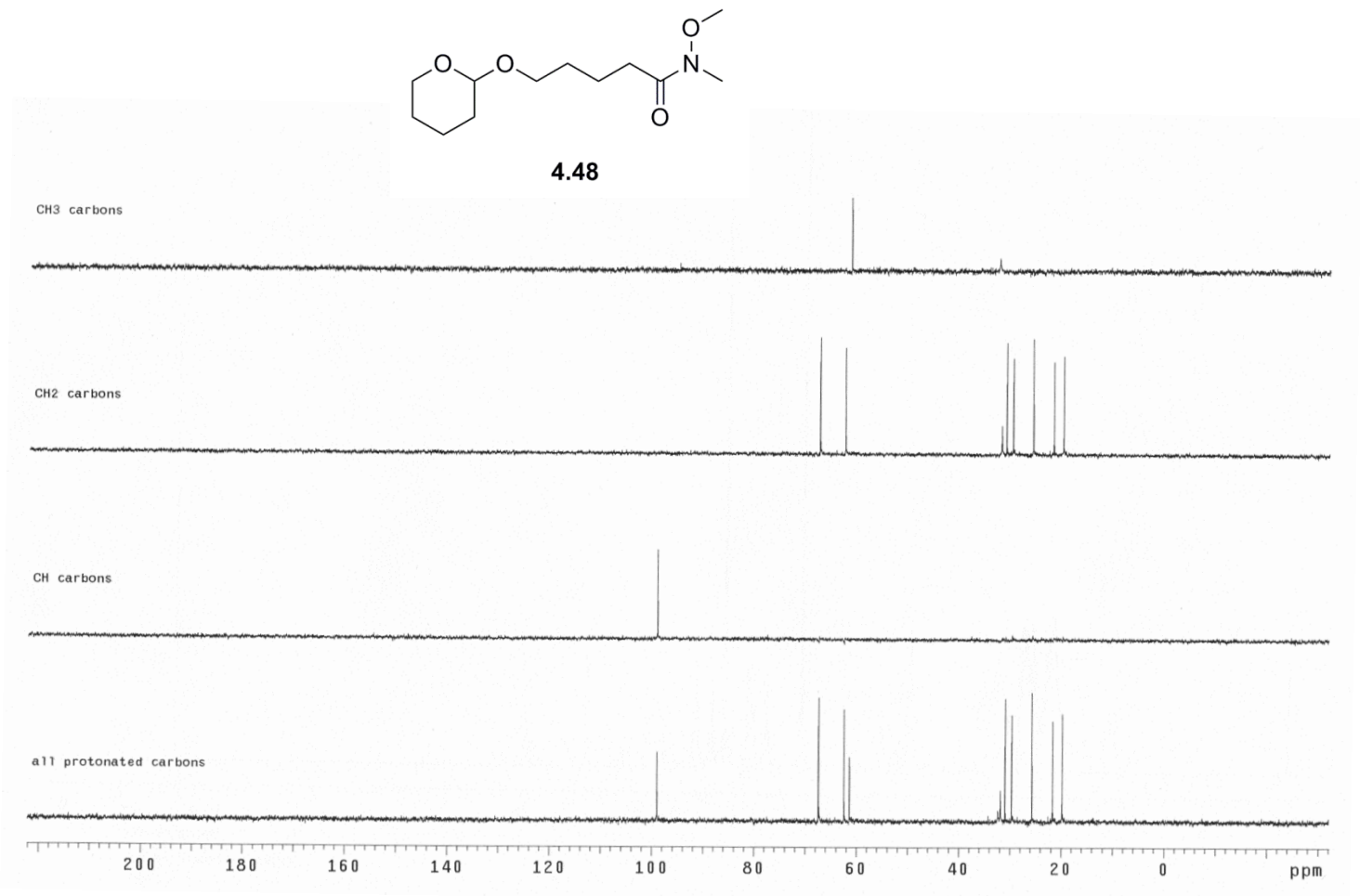

HO
O
N
O

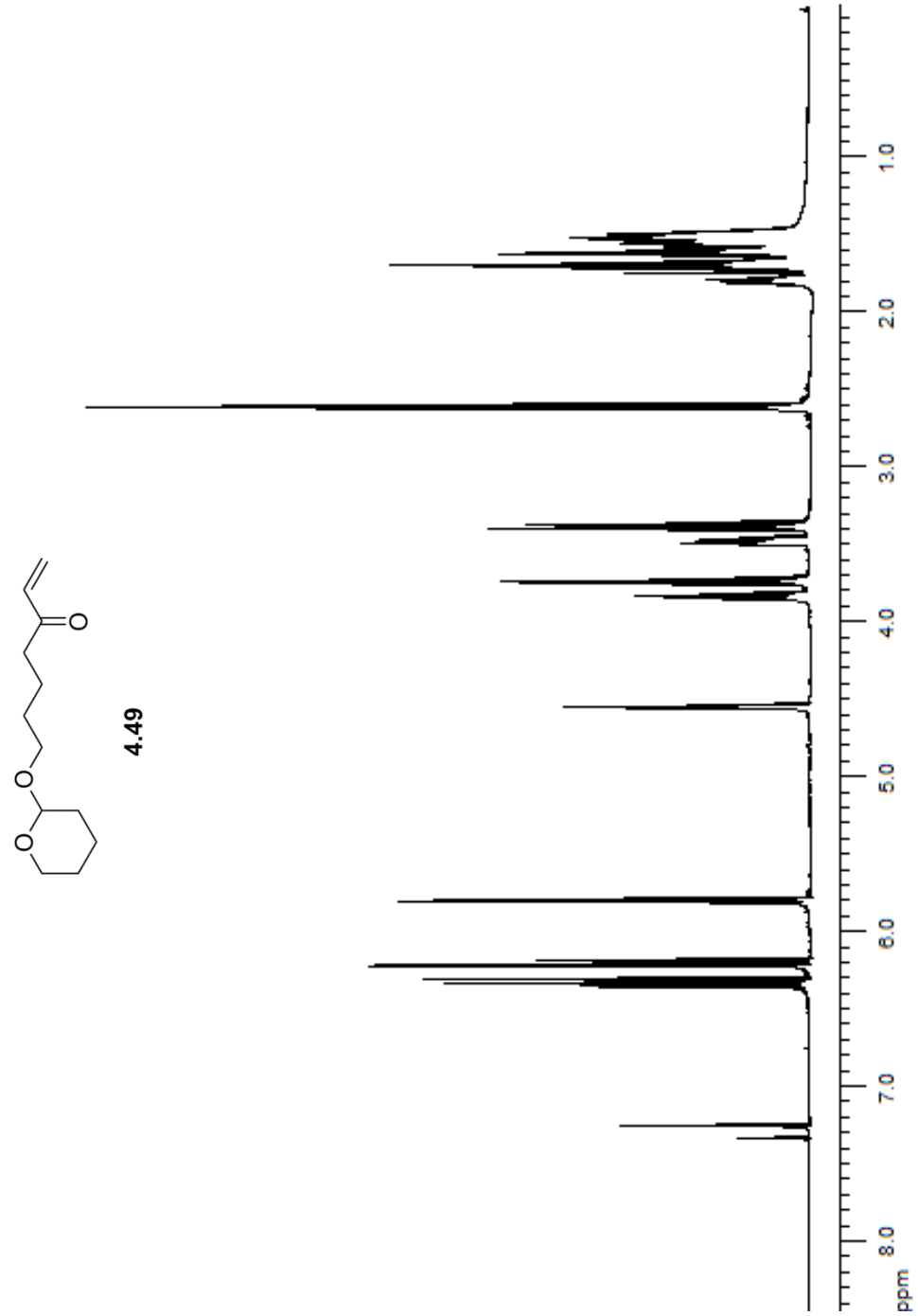
4.47

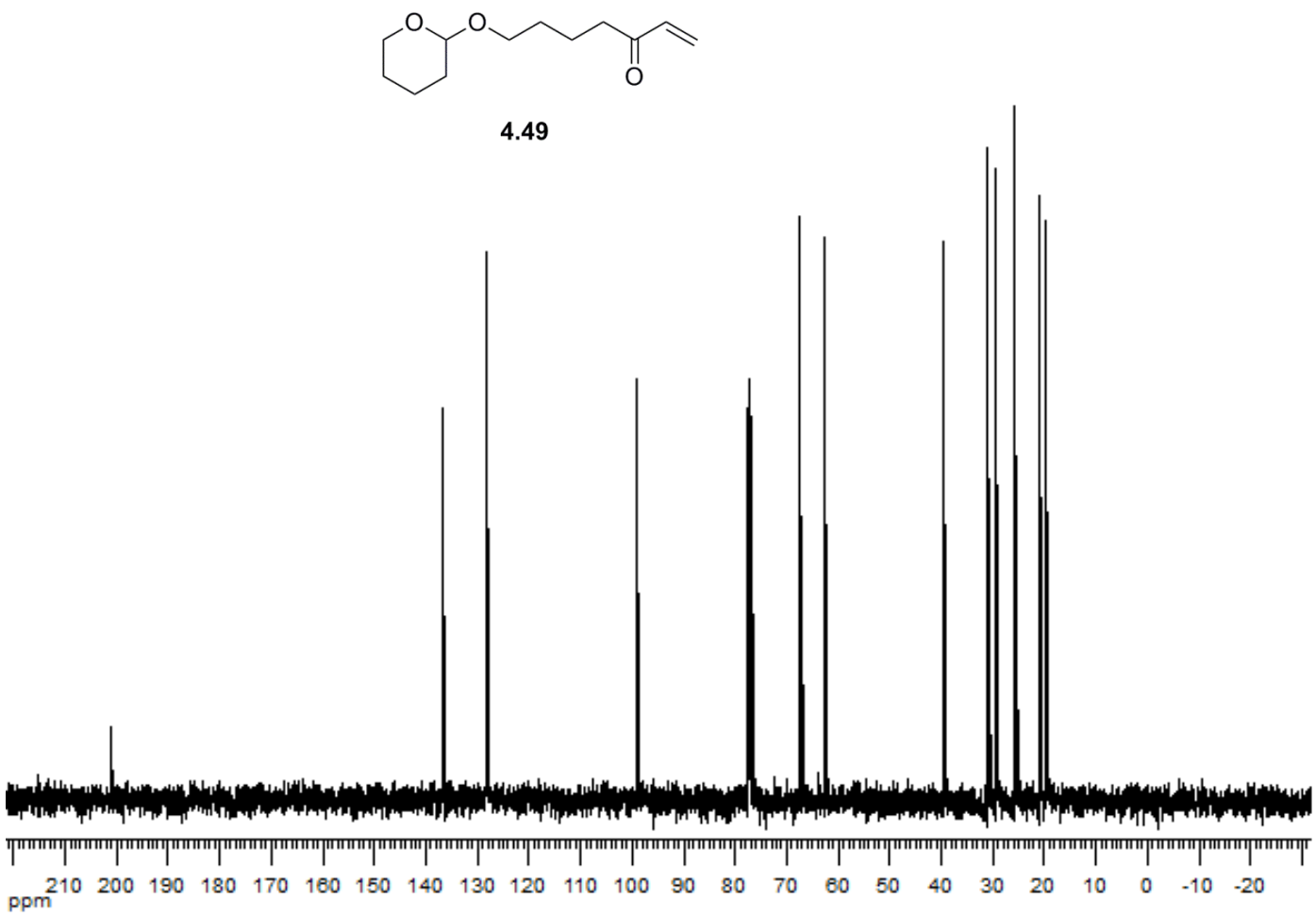

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm

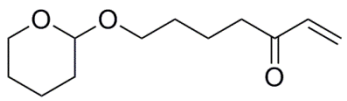

O
N
O
O
O
4.48
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


4.48
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
ppm


O
O
O
N
O
4.48
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

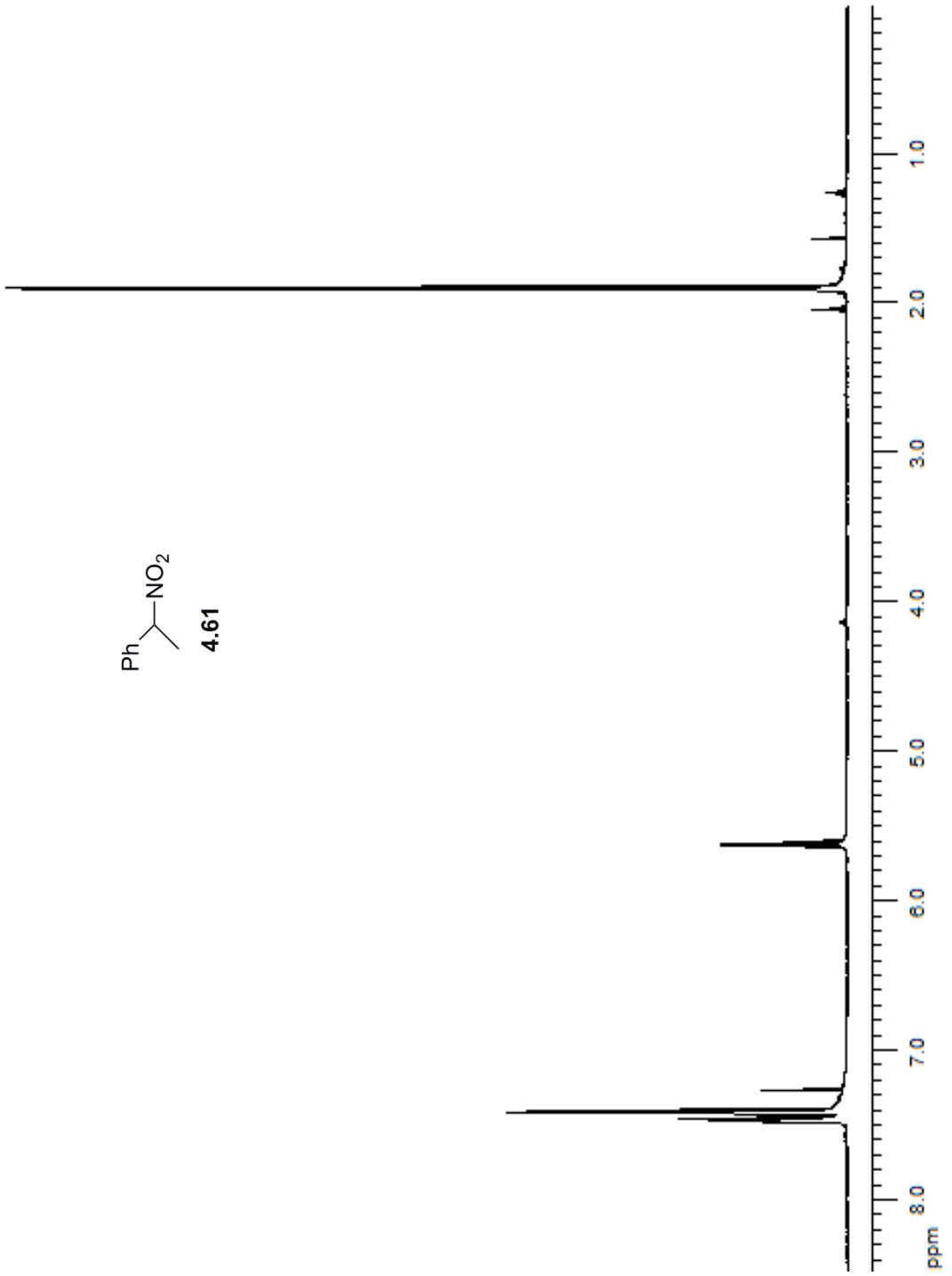

4.49
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm

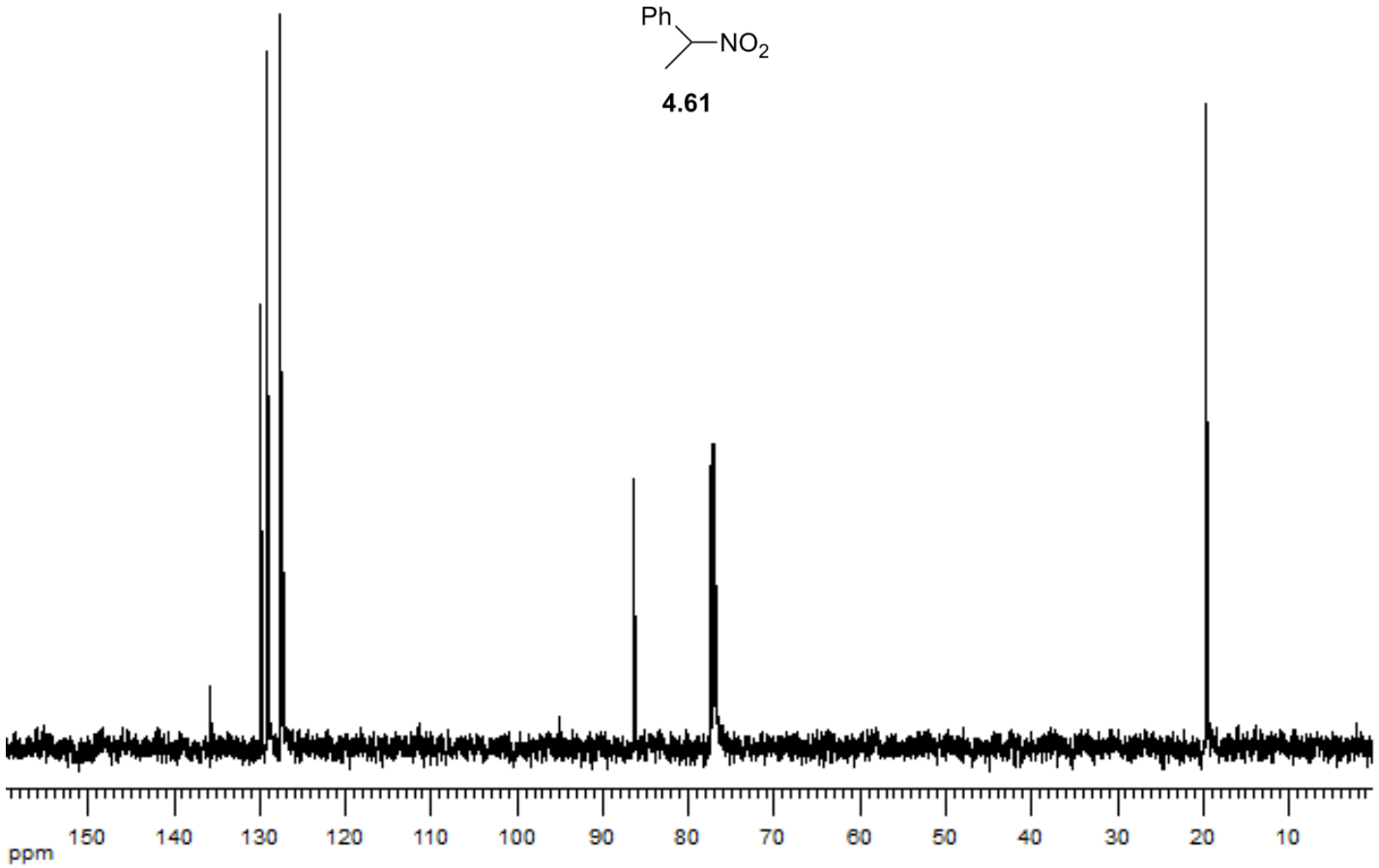

O
O
O
4.49
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm

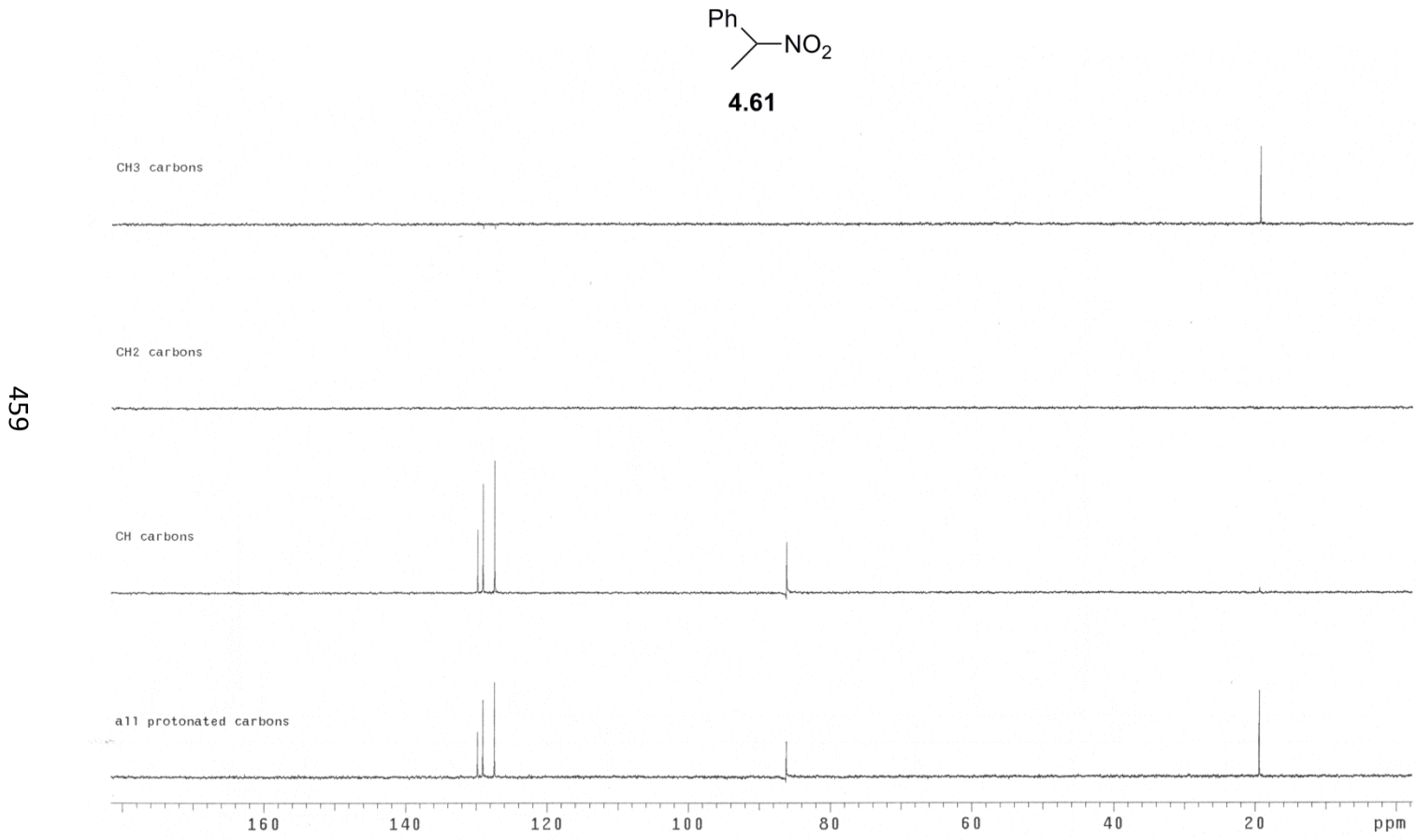


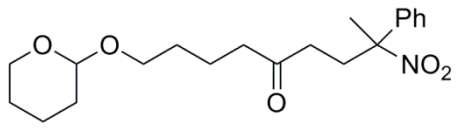
4.49

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
ppm

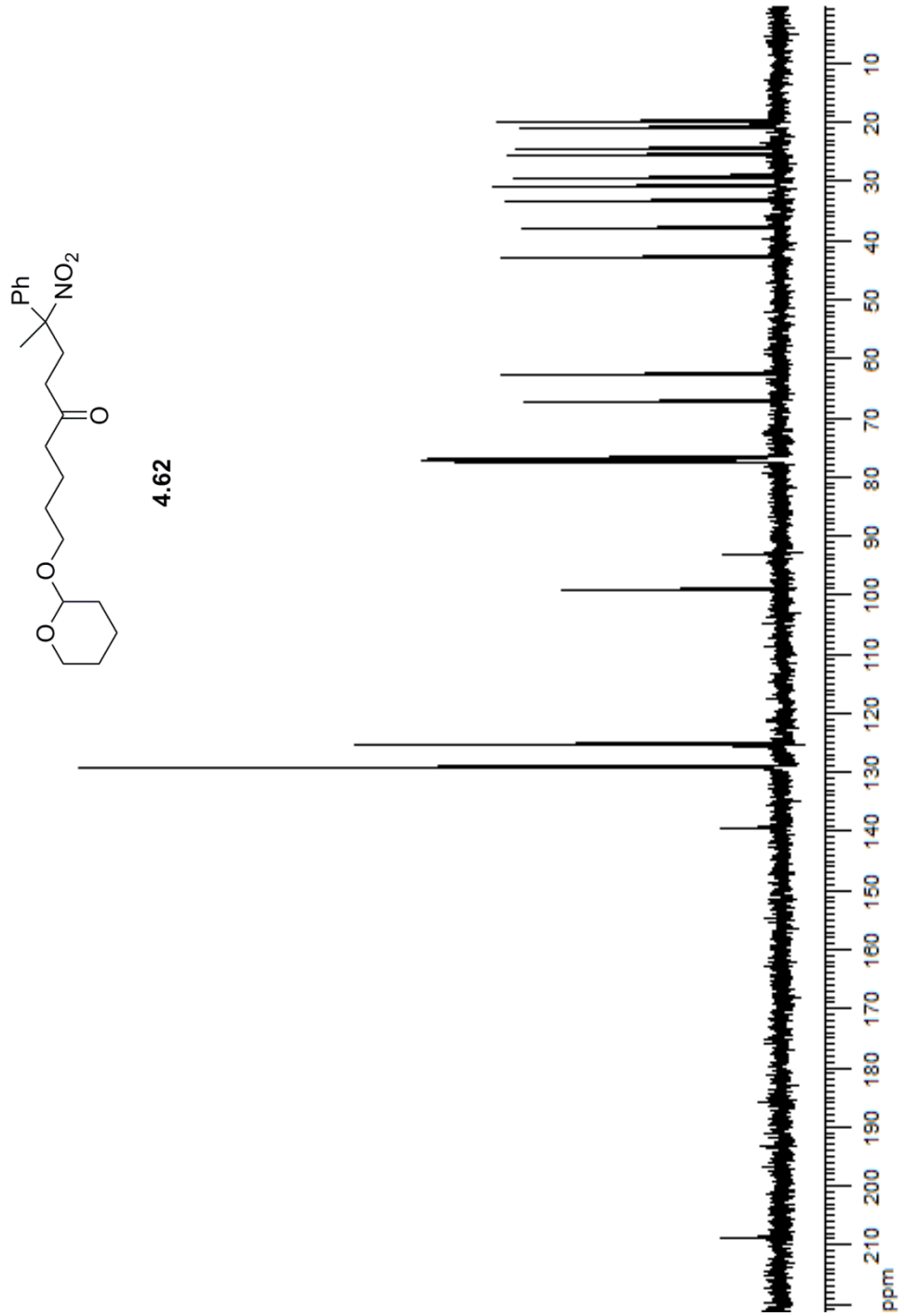

Ph
NO2
4.61
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm

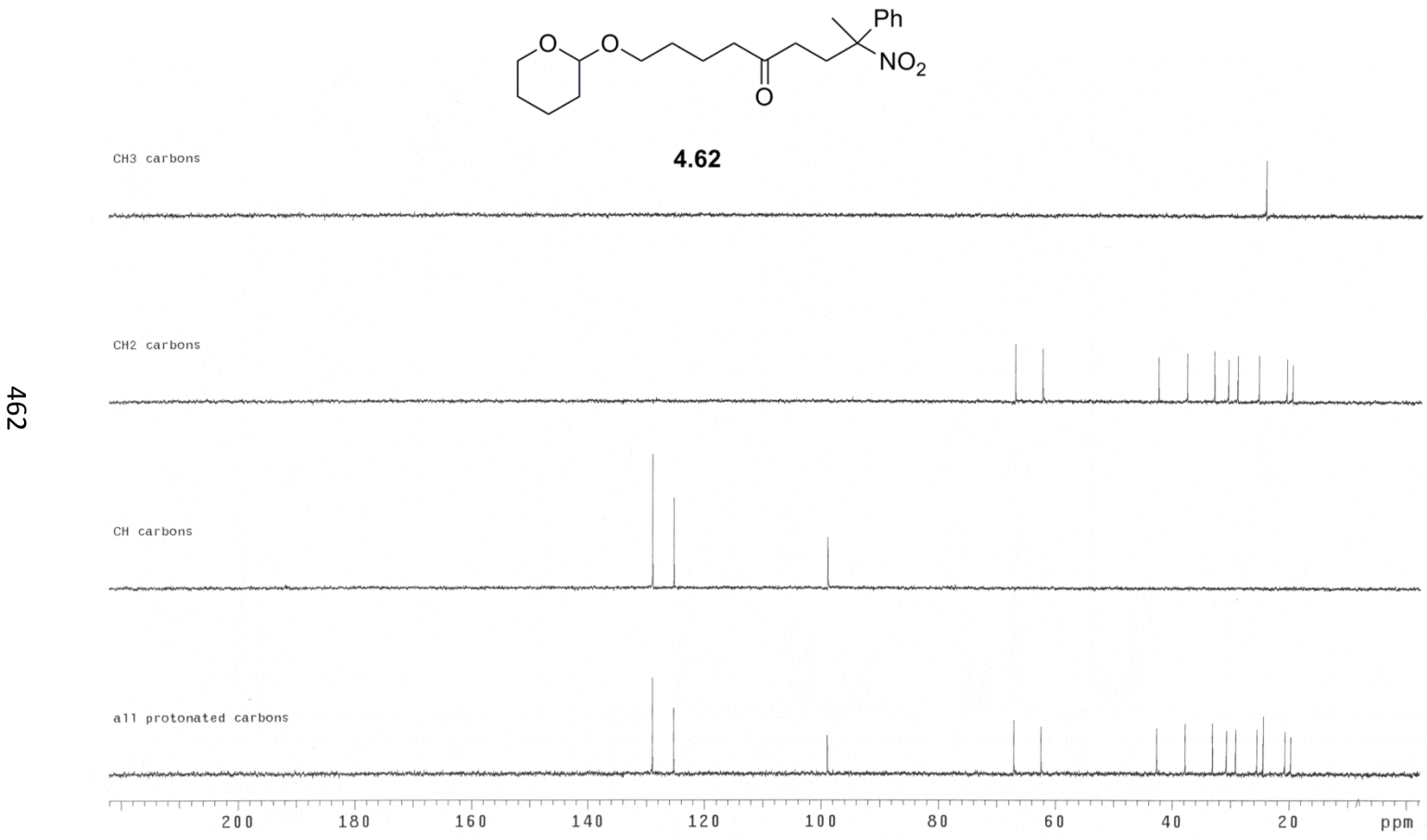

Ph
NO2
4.61
ppm
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

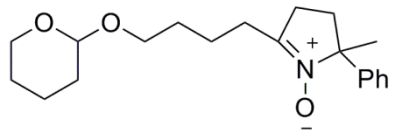

Ph
NO2
4.61
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm



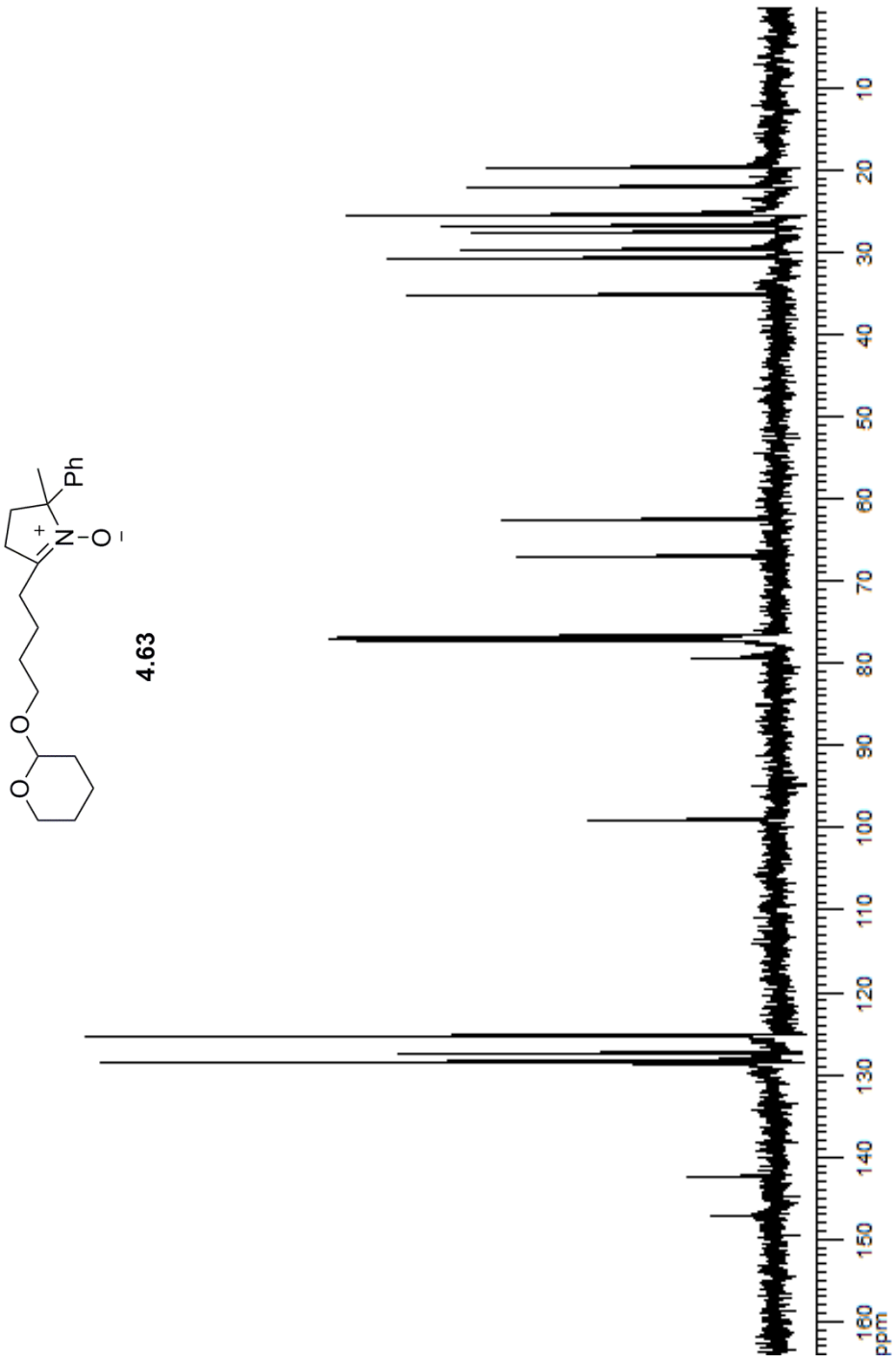
4.62

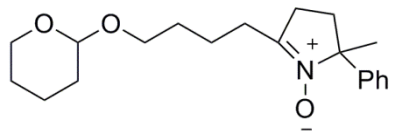

Ph
NO2
O
O
O
4.62
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
ppm


Ph
NO2
O
O
O
4.62
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
ppm

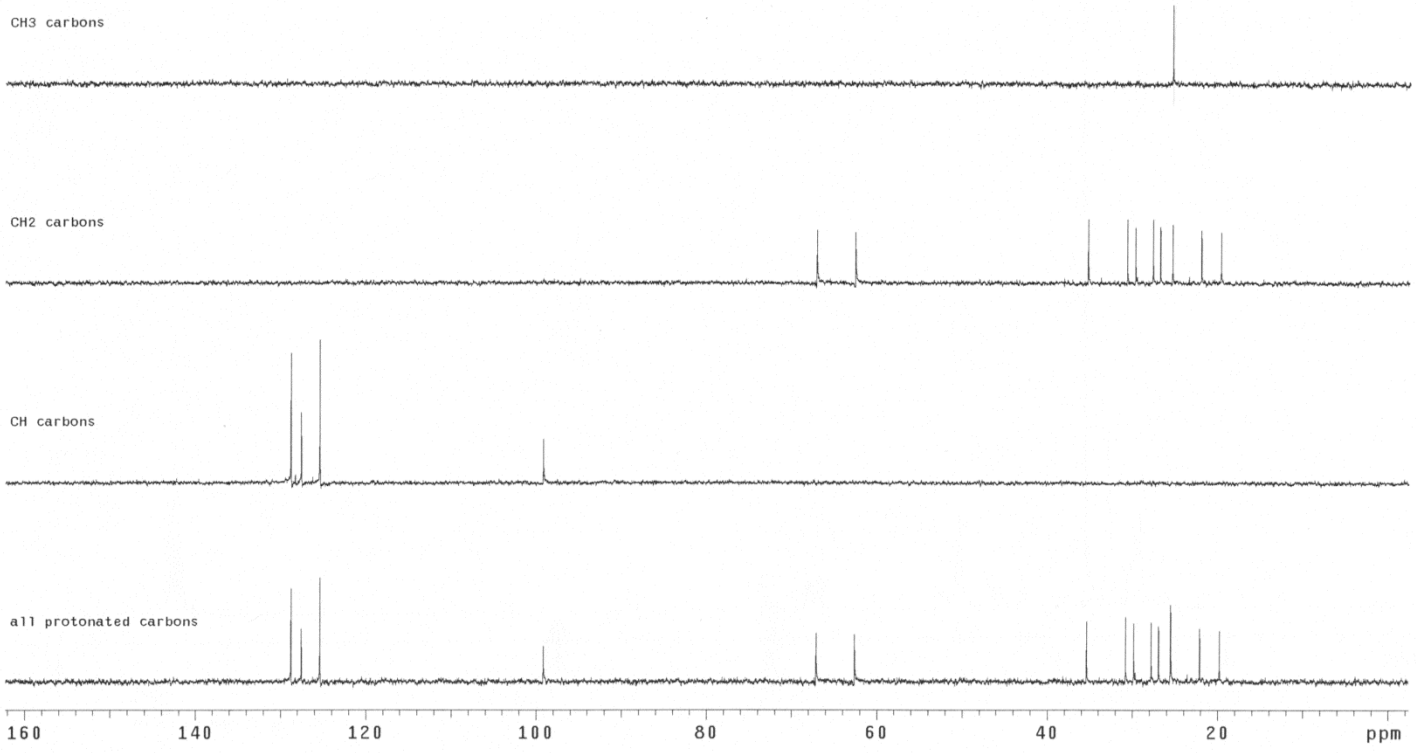


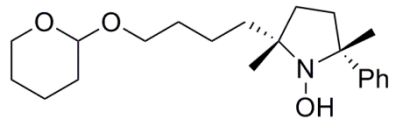
4.63


Ph
N
O
O
O
4.63
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm

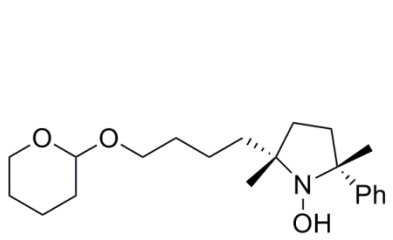

O
O
N
+
O
−
Ph

4.63

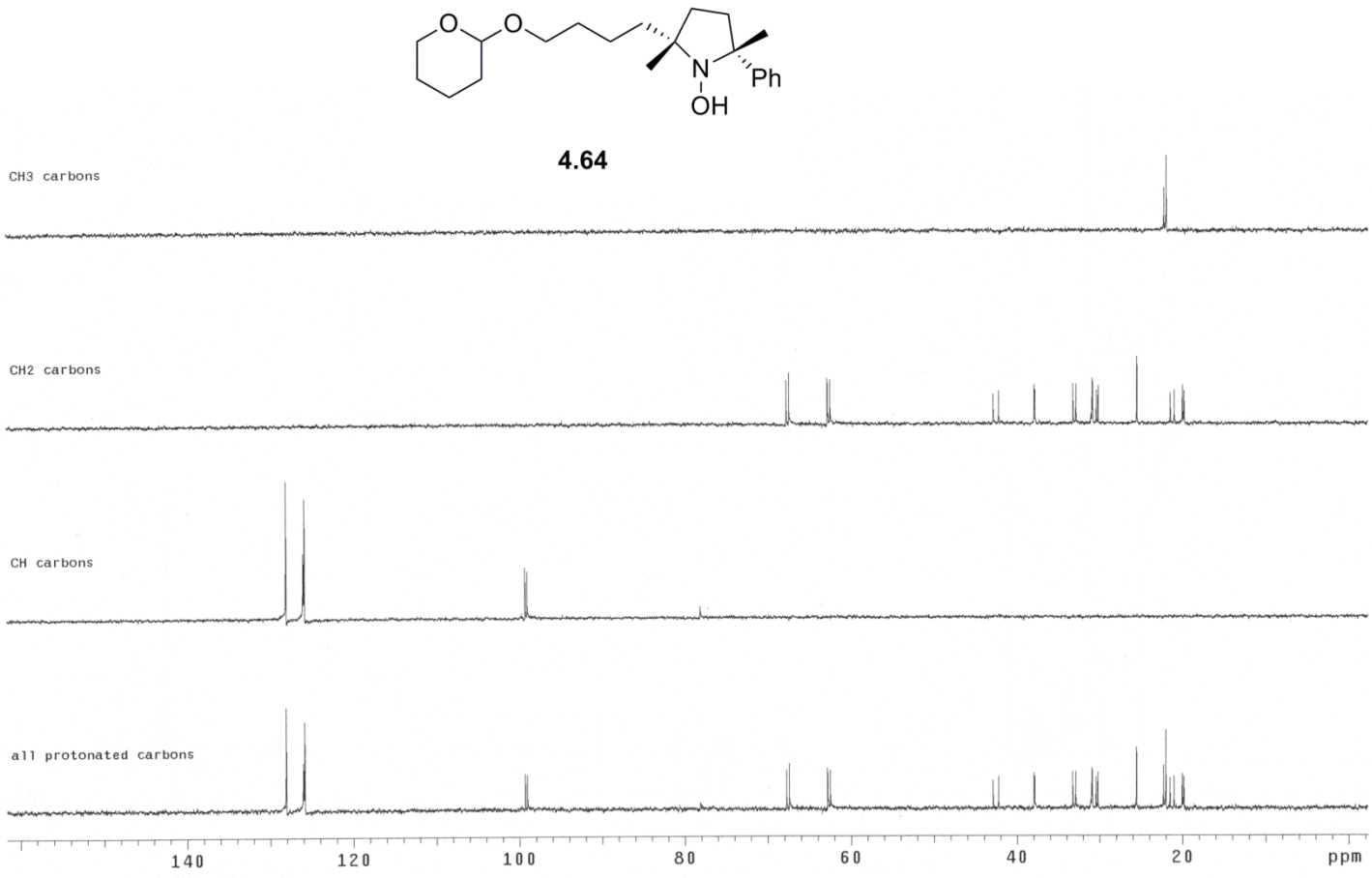

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm



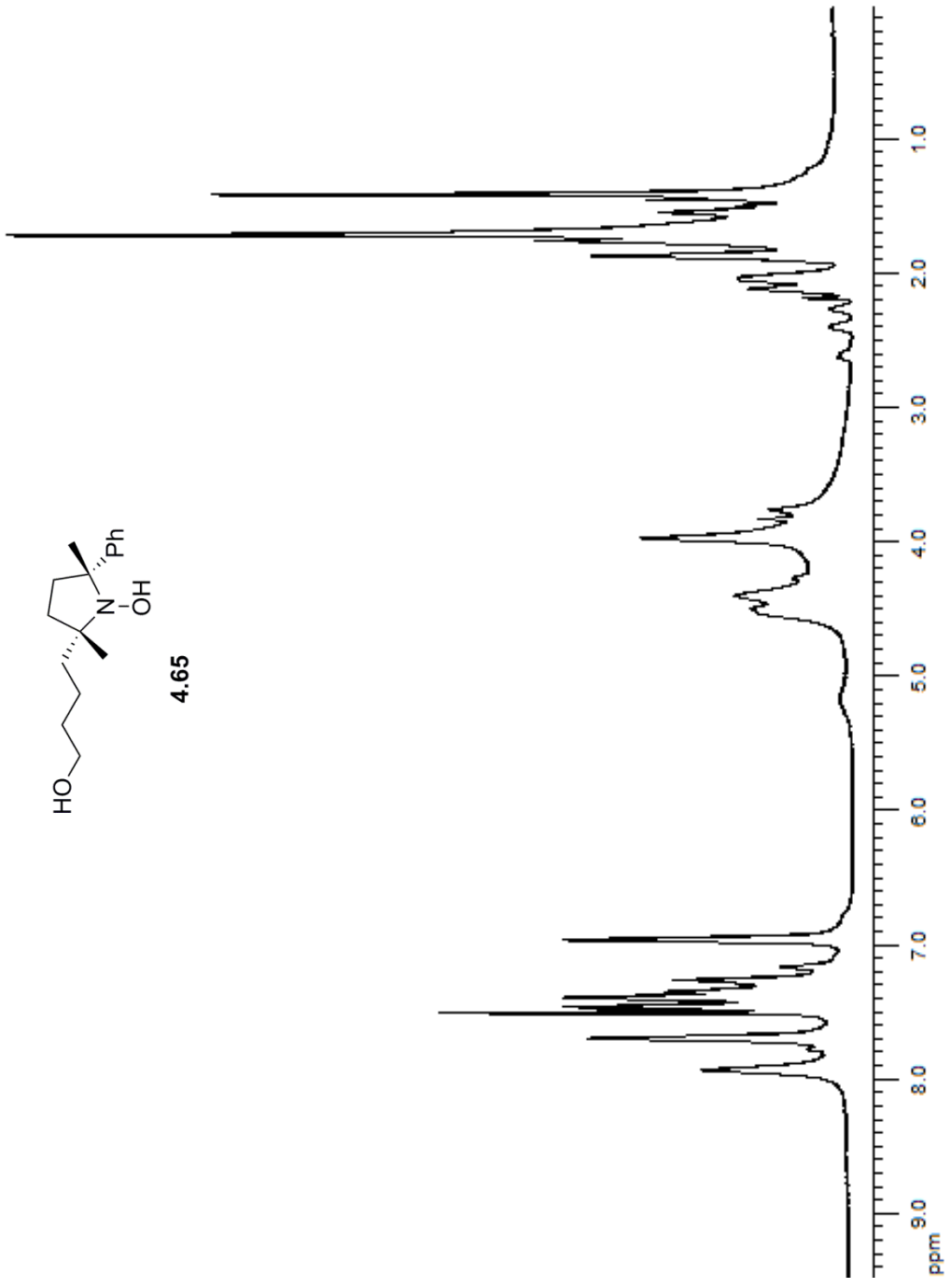
4.64

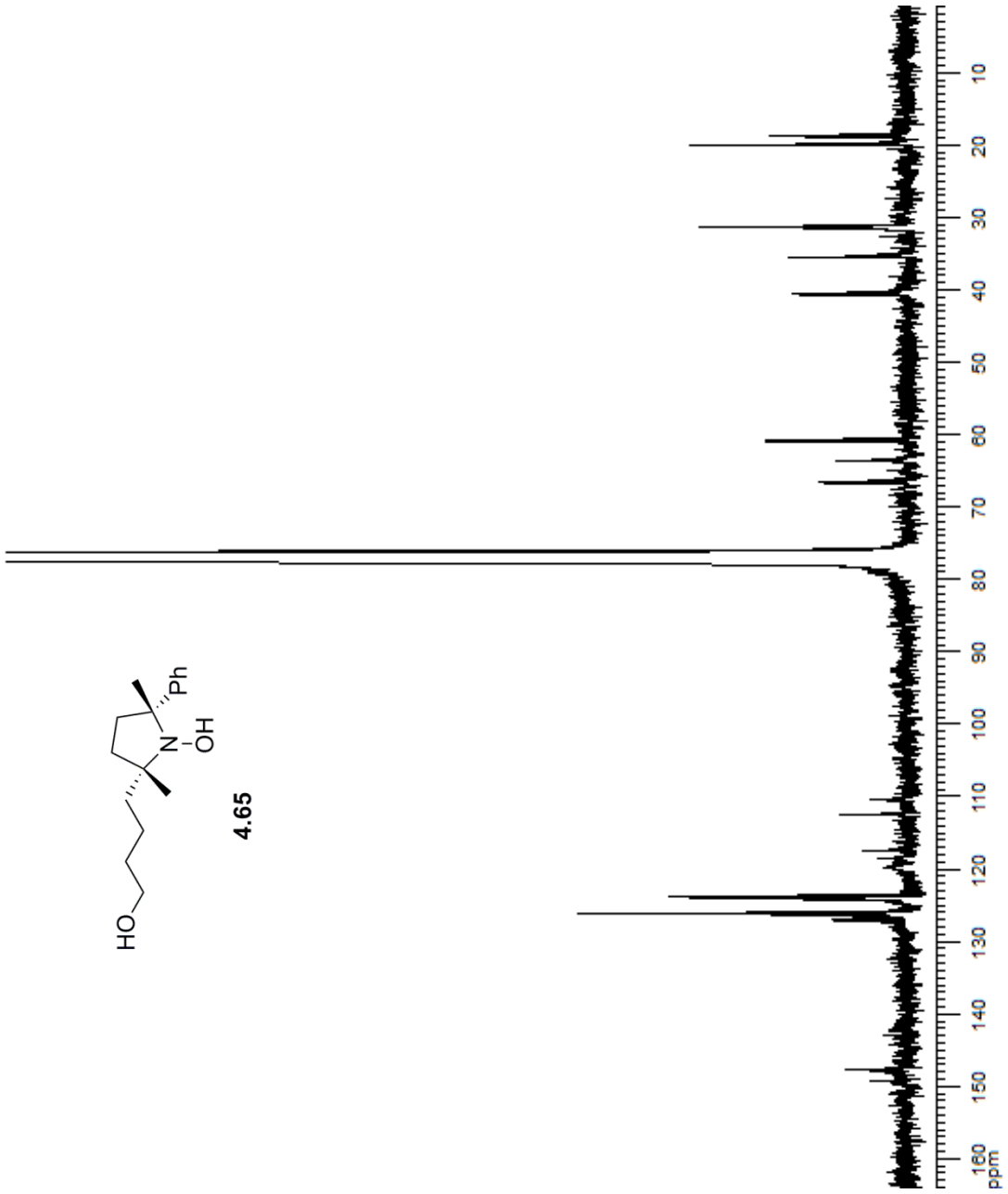


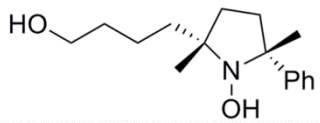
4.64


O
O
N
OH
Ph
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
140
120
100
80
60
40
20
ppm

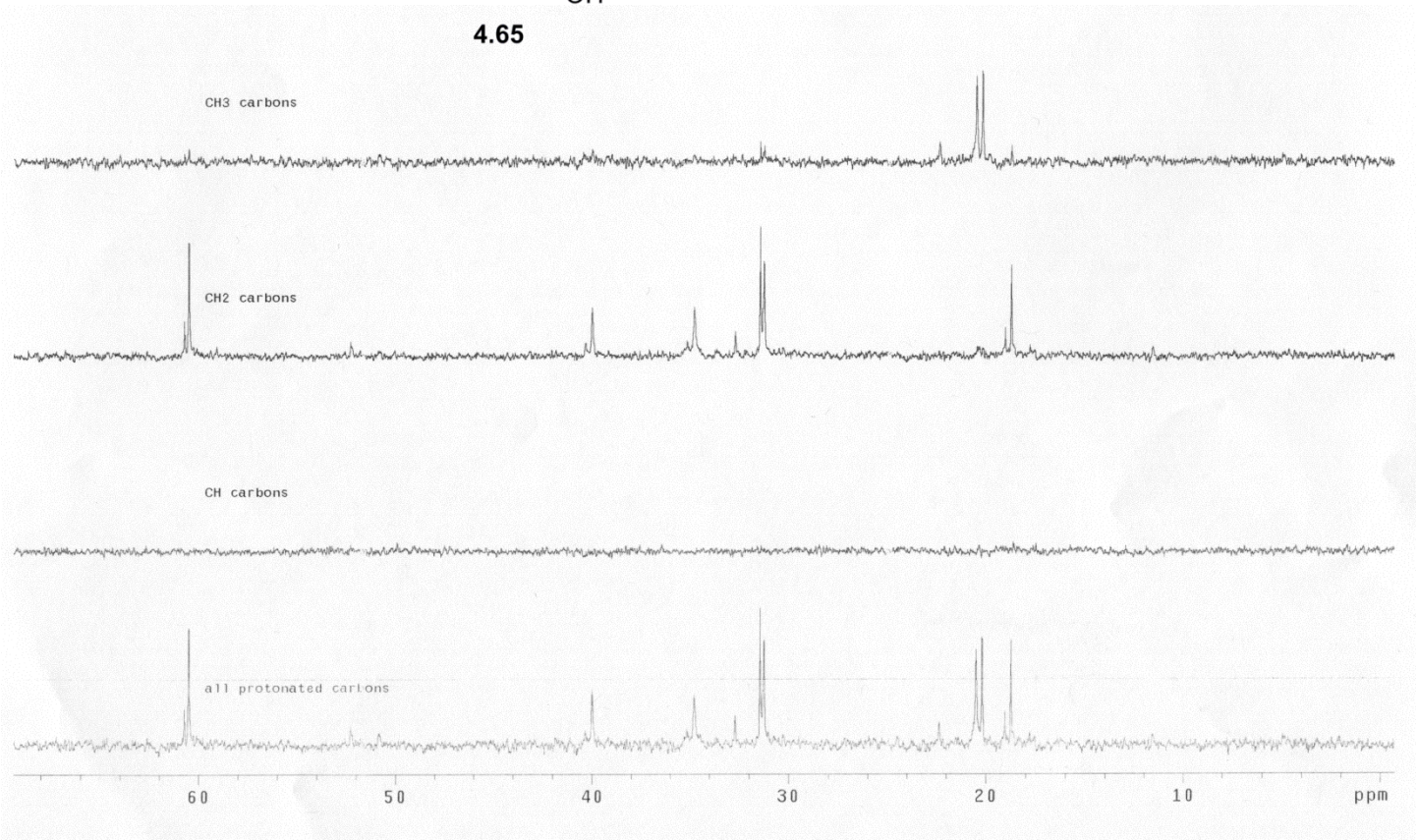
4.64

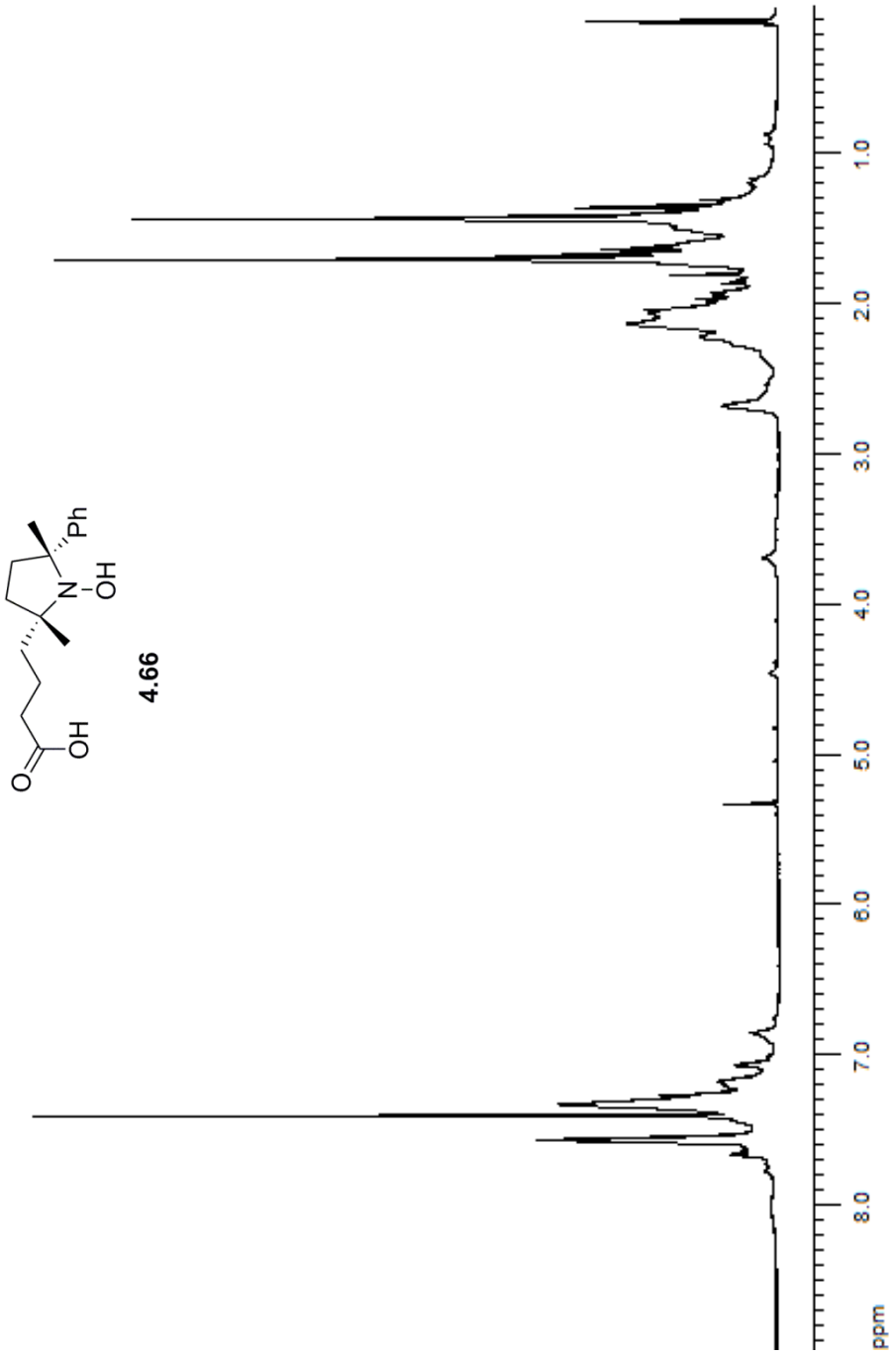

Ph
N
OH
HO
4.65
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm

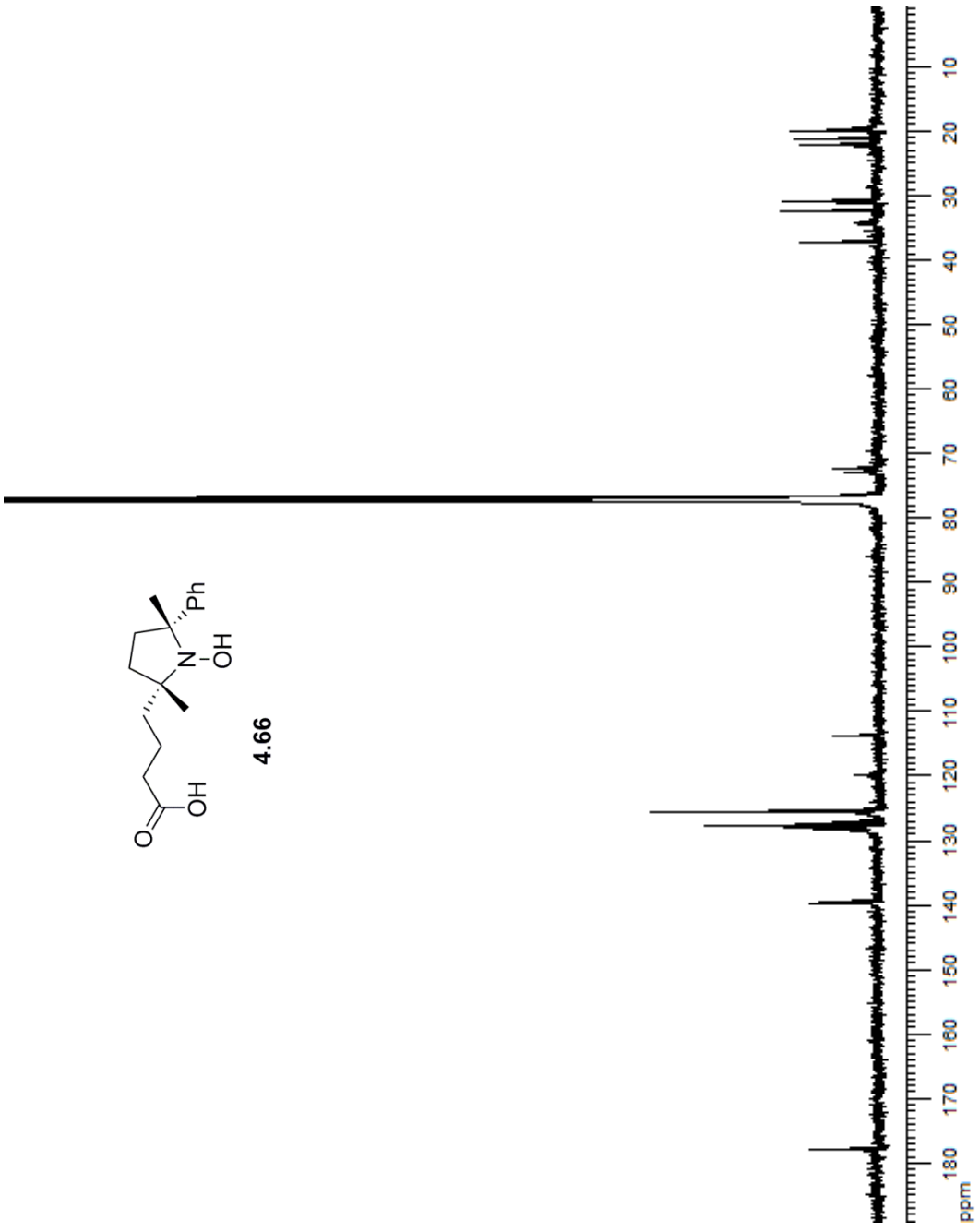

Ph
N
OH
HO
4.65
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm

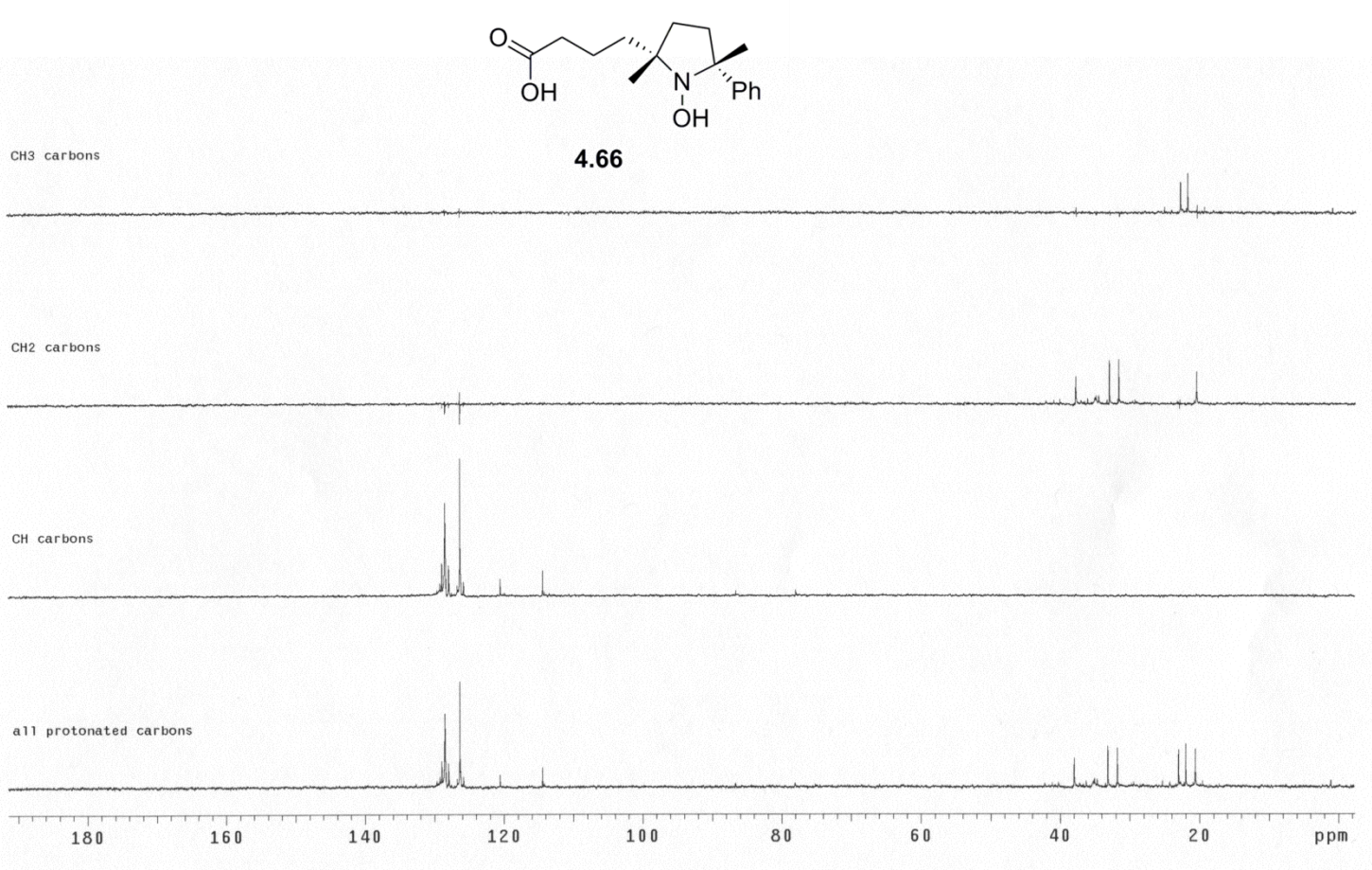

HO
N
OH
Ph

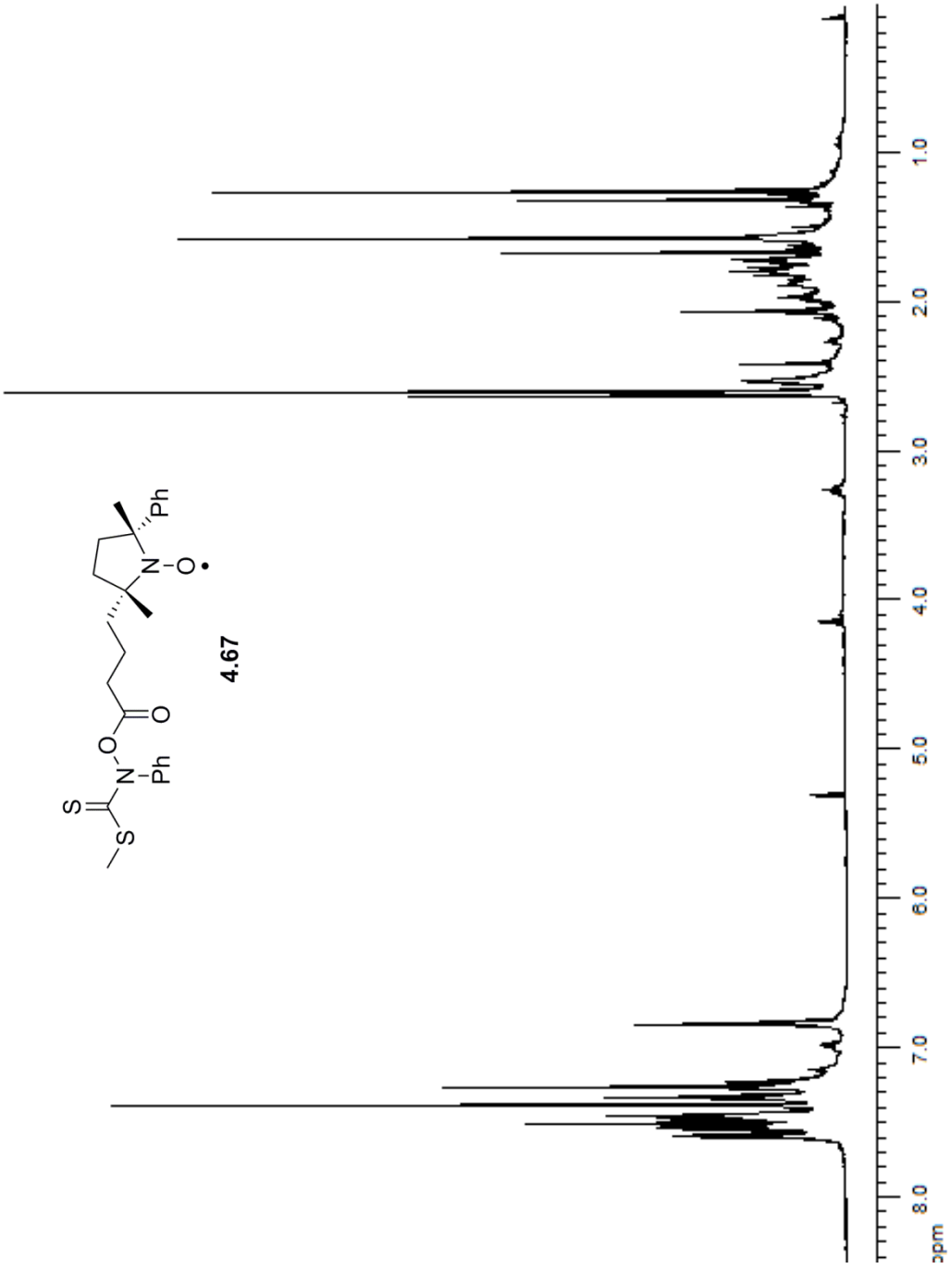
4.65


CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
60
50
40
30
20
10
ppm

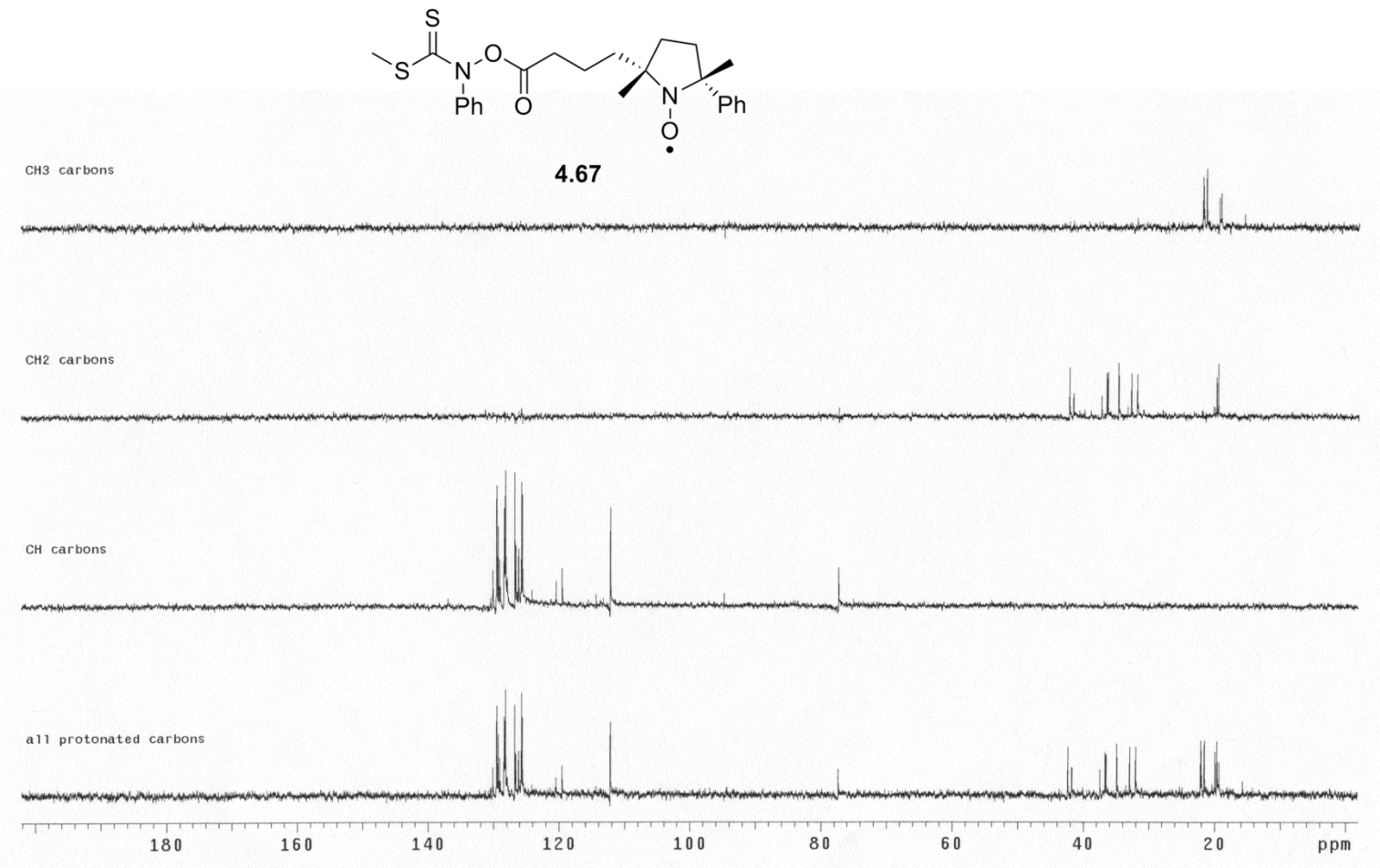

Ph
N
OH
OH
O
4.66
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


Ph
N
OH
O
OH
4.66
ppm

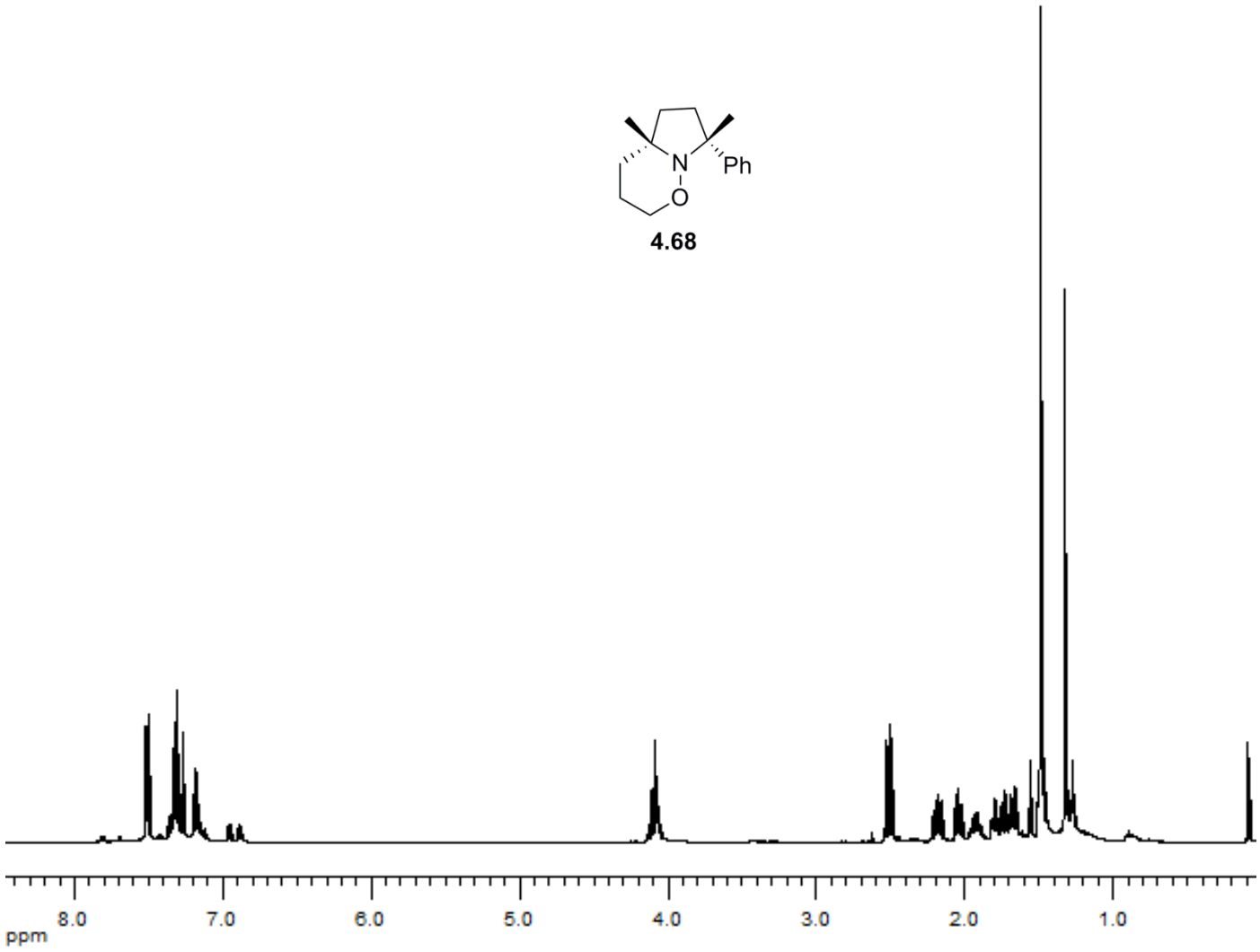

O
OH
N
OH
Ph
4.66
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm


Ph
N
O
O
O
N
Ph
S
S
4.67
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

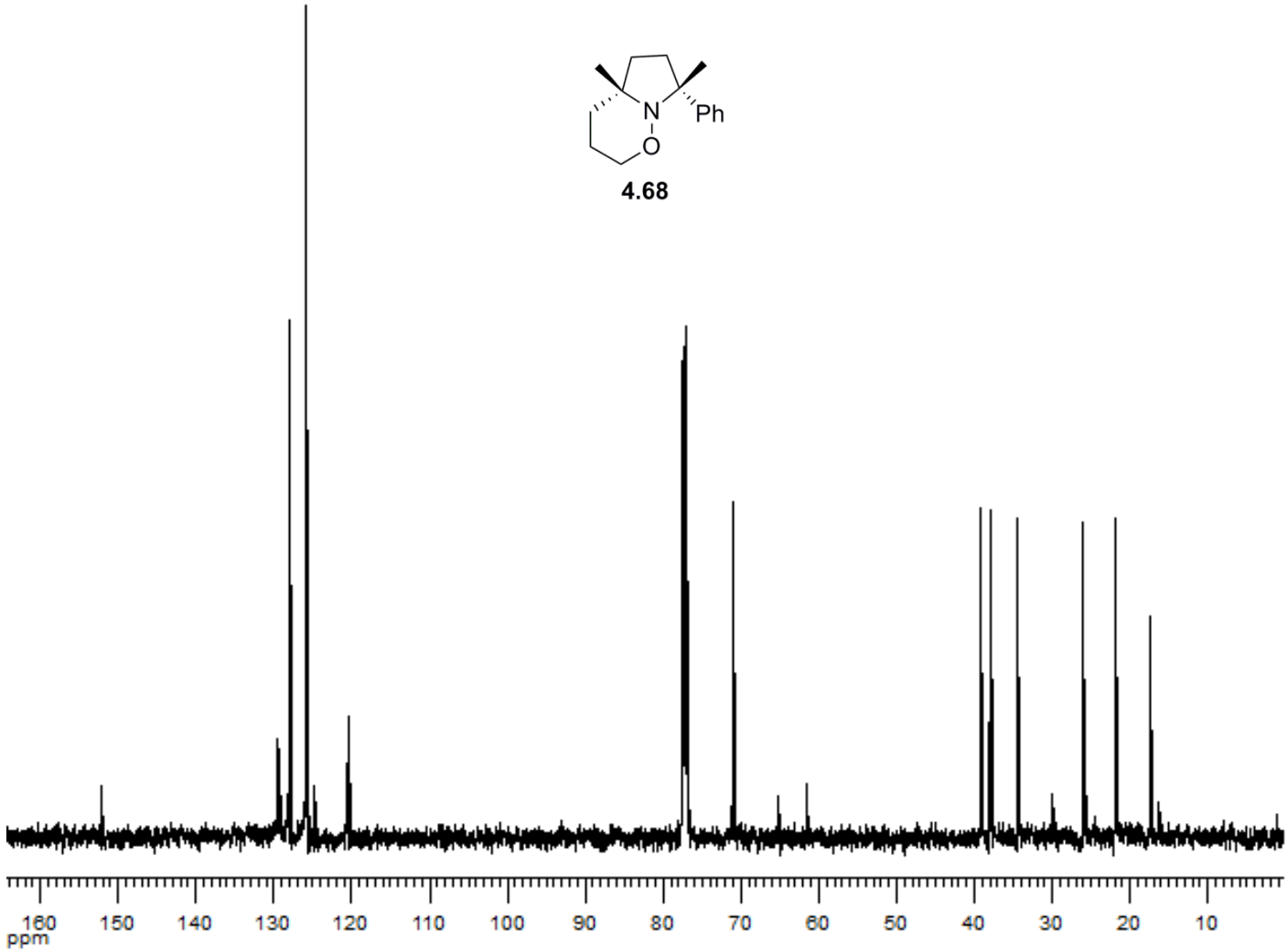
Ph
N
O
O
O
N
Ph
S
S
4.67
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


S
S
N
O
Ph
O
N
O
Ph
4.67
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm

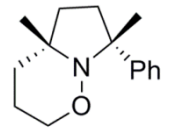
Ph
N
O
S
S
Ph
N
O
O
O
4.67
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
44
42
40
38
36
34
32
30
28
26
24
22
20
ppm



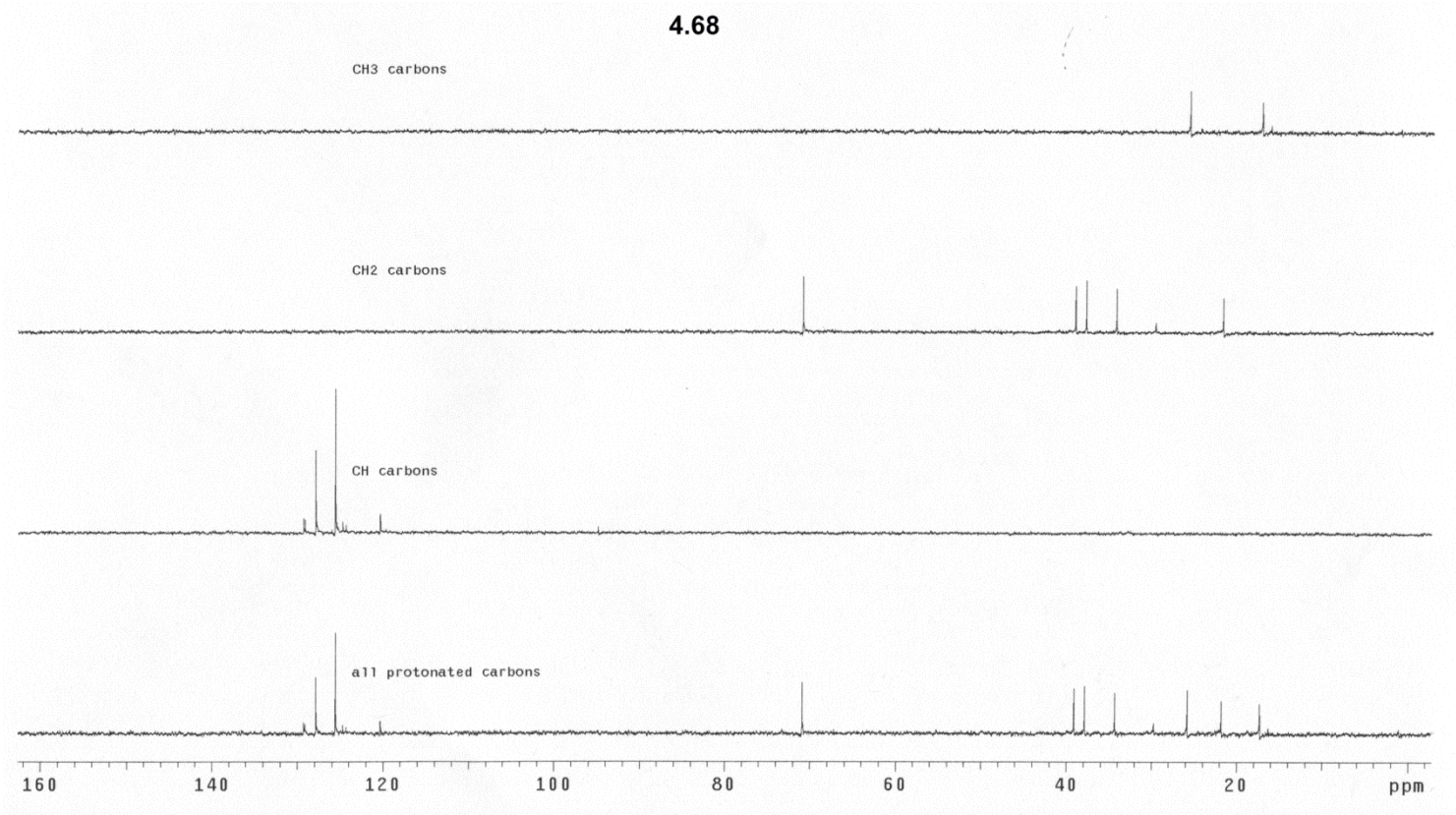
4.68



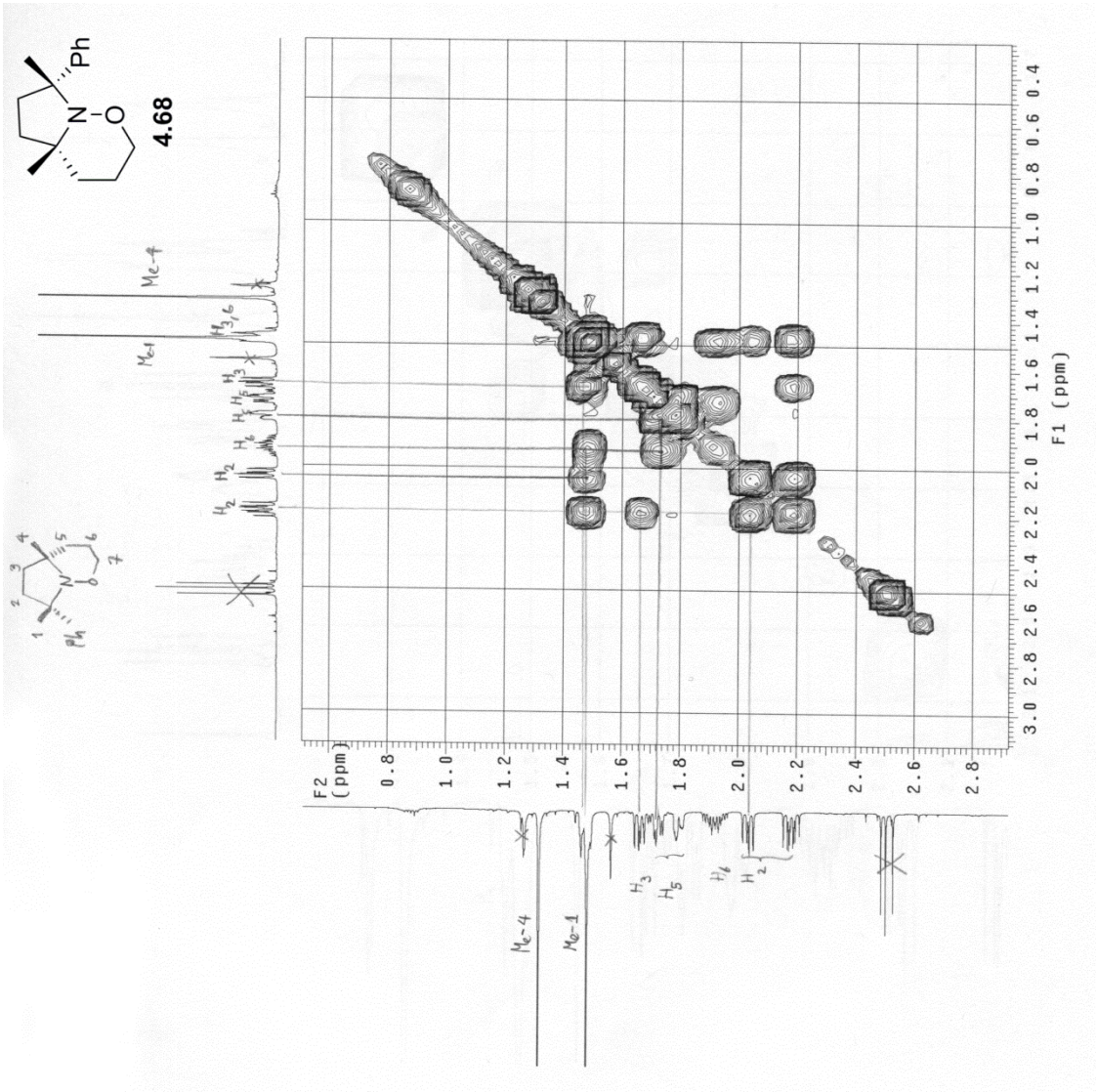
4.68


N
O
Ph

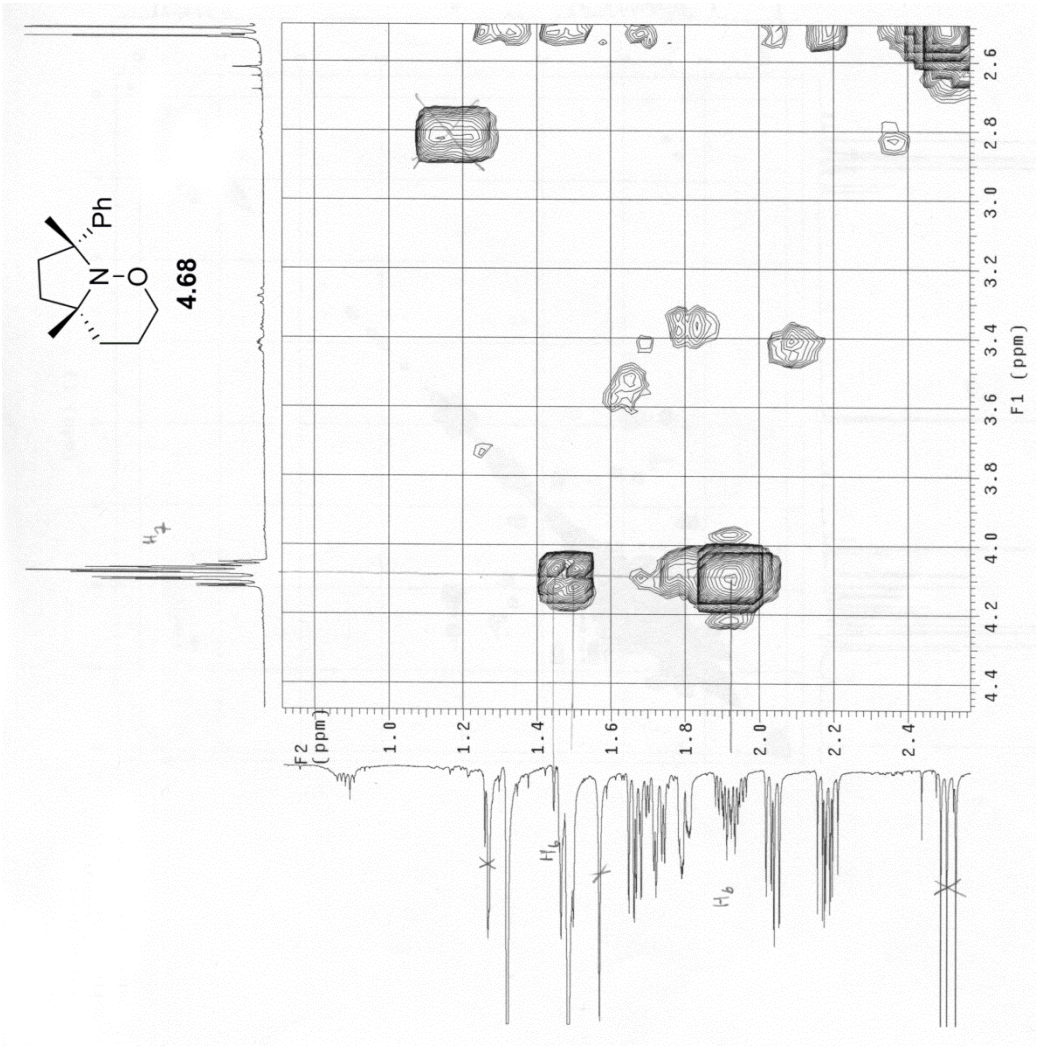
4.68


CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm

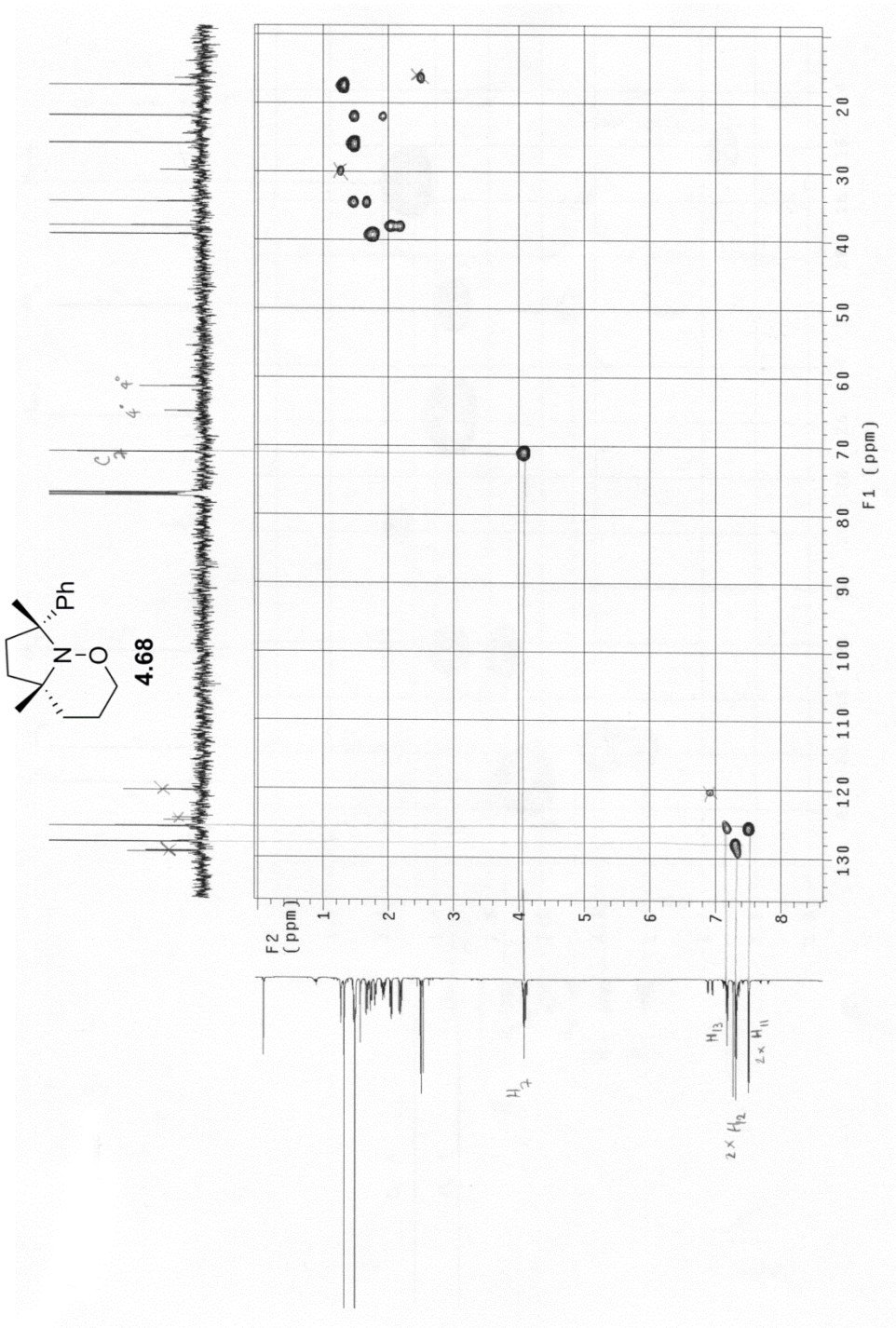
COSY (1)



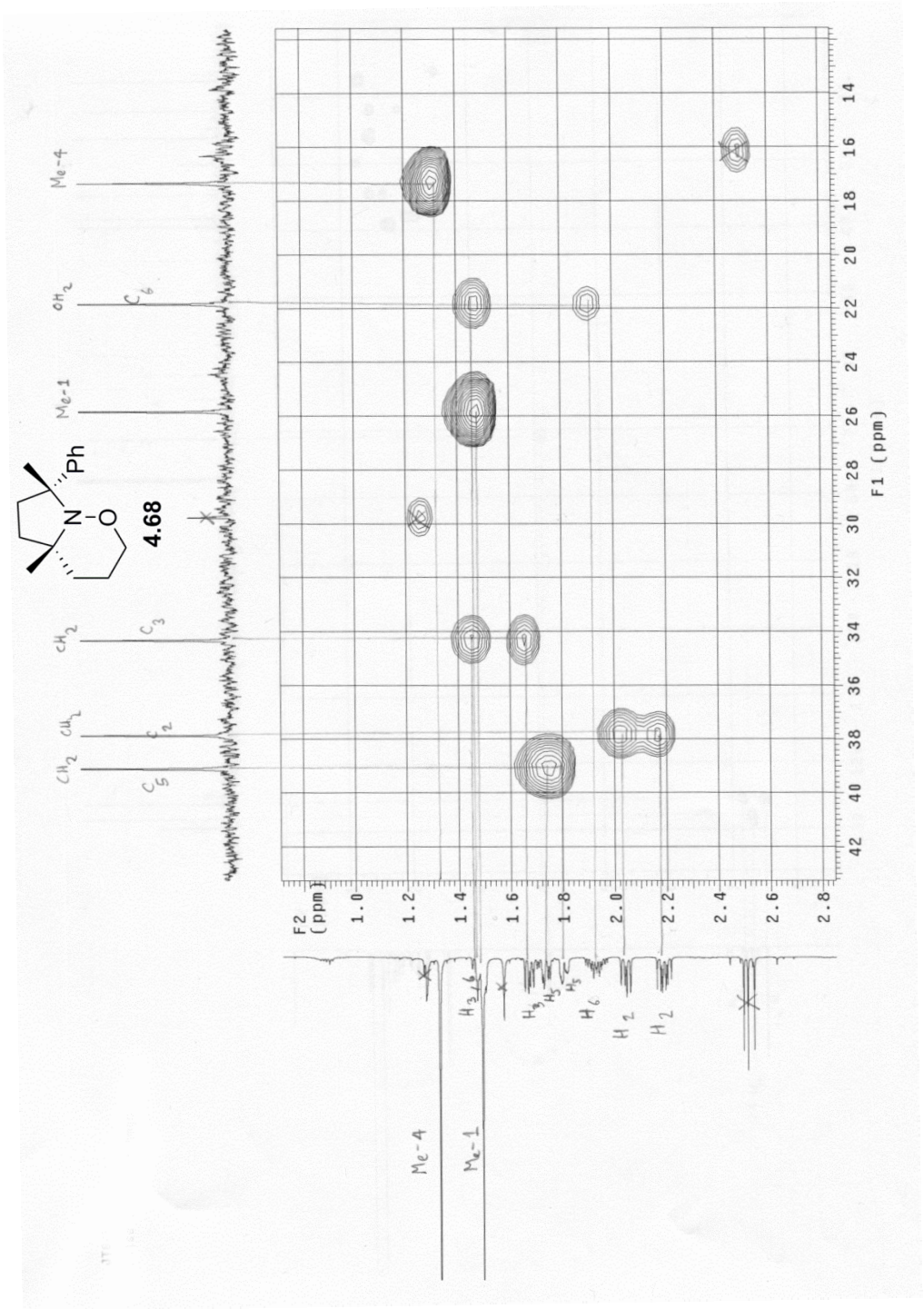
COSY(2)



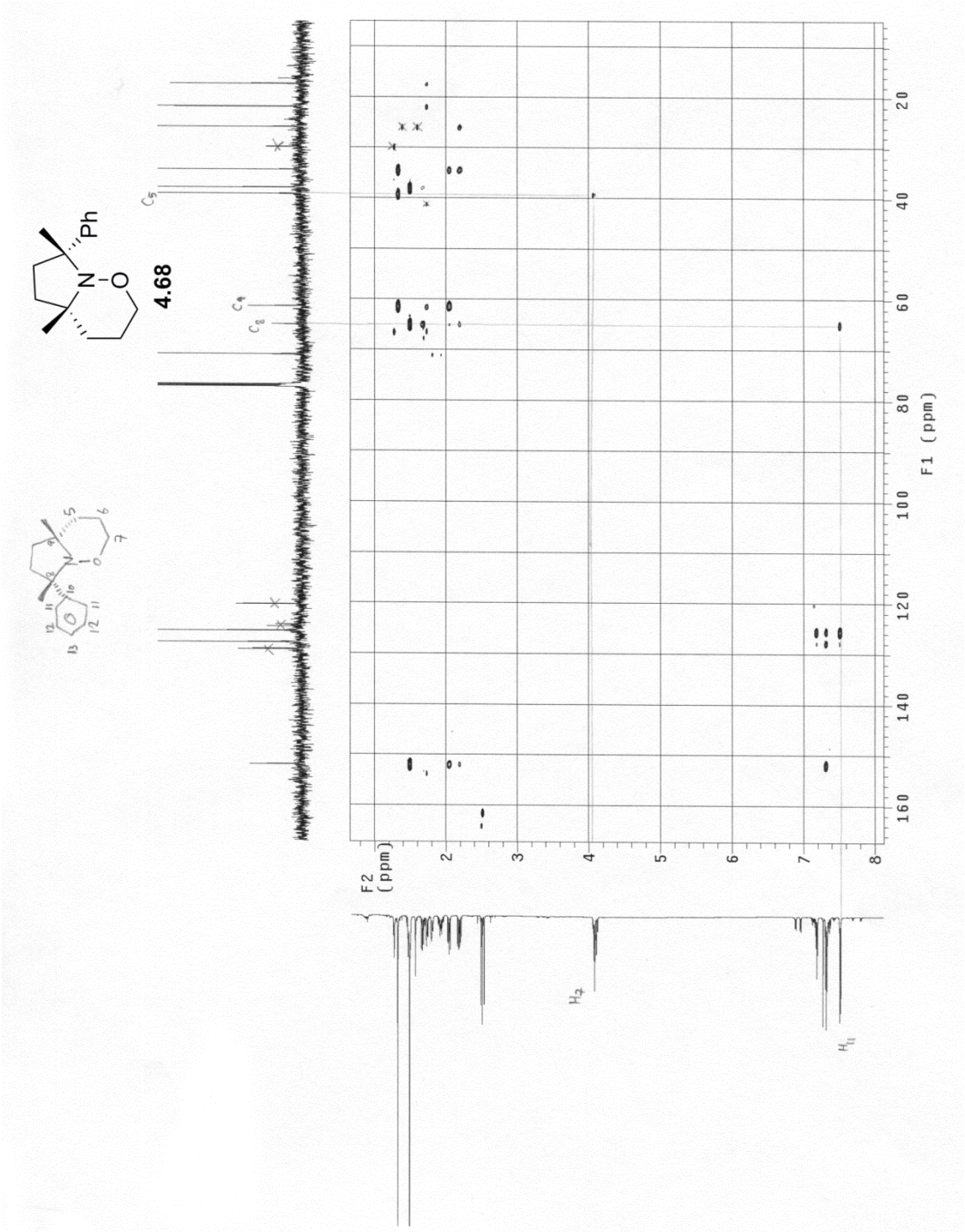
HMQC(1)



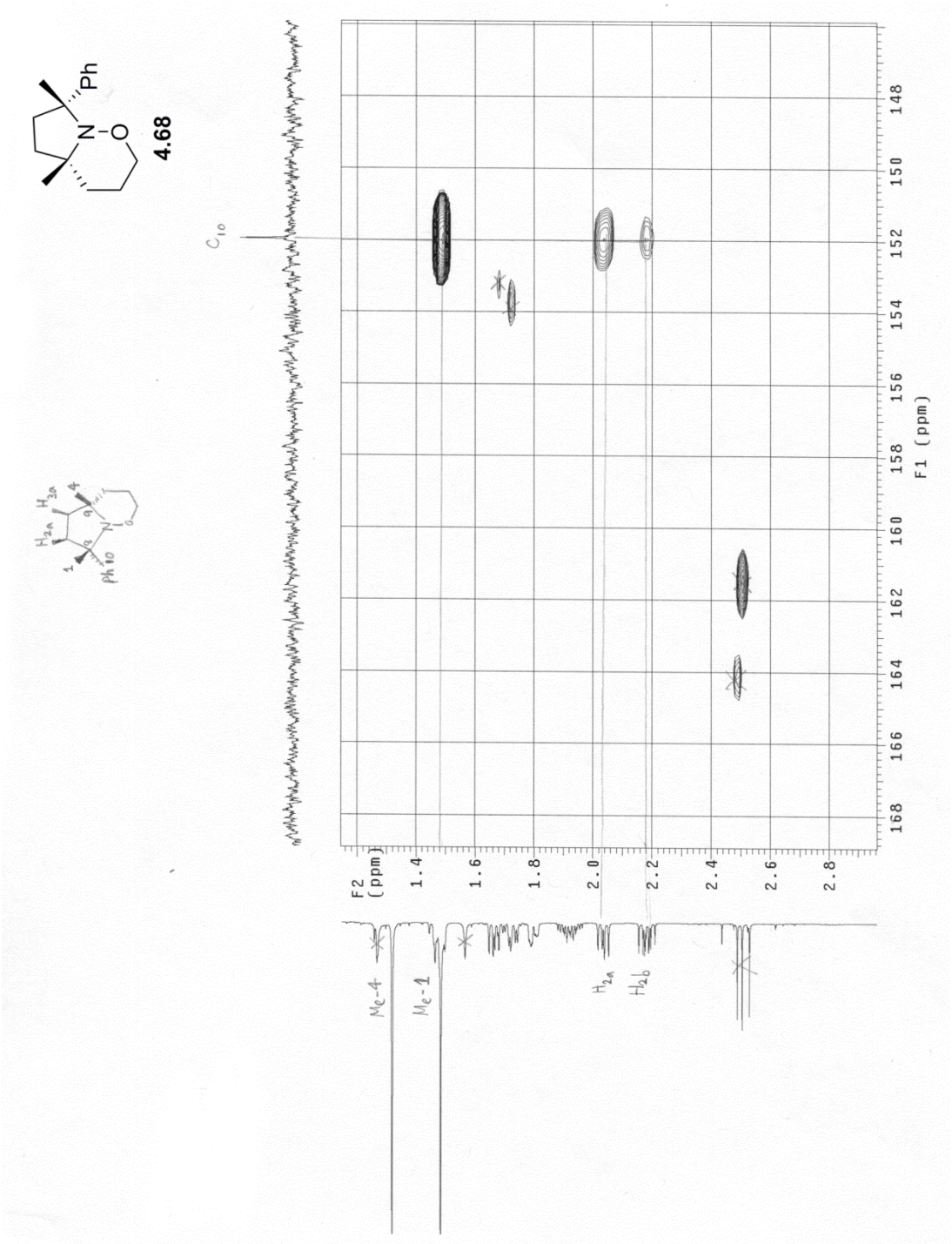
HMQC(2)


Ph
N
O
4.68
Me-4
Me-1
CH2
CH2
CH2
CH2
C6
C3
C2
C5
F2 (ppm)
F1 (ppm)
Me-4
Me-1
H3,6
H3
H5
H5
H6
H2
H2

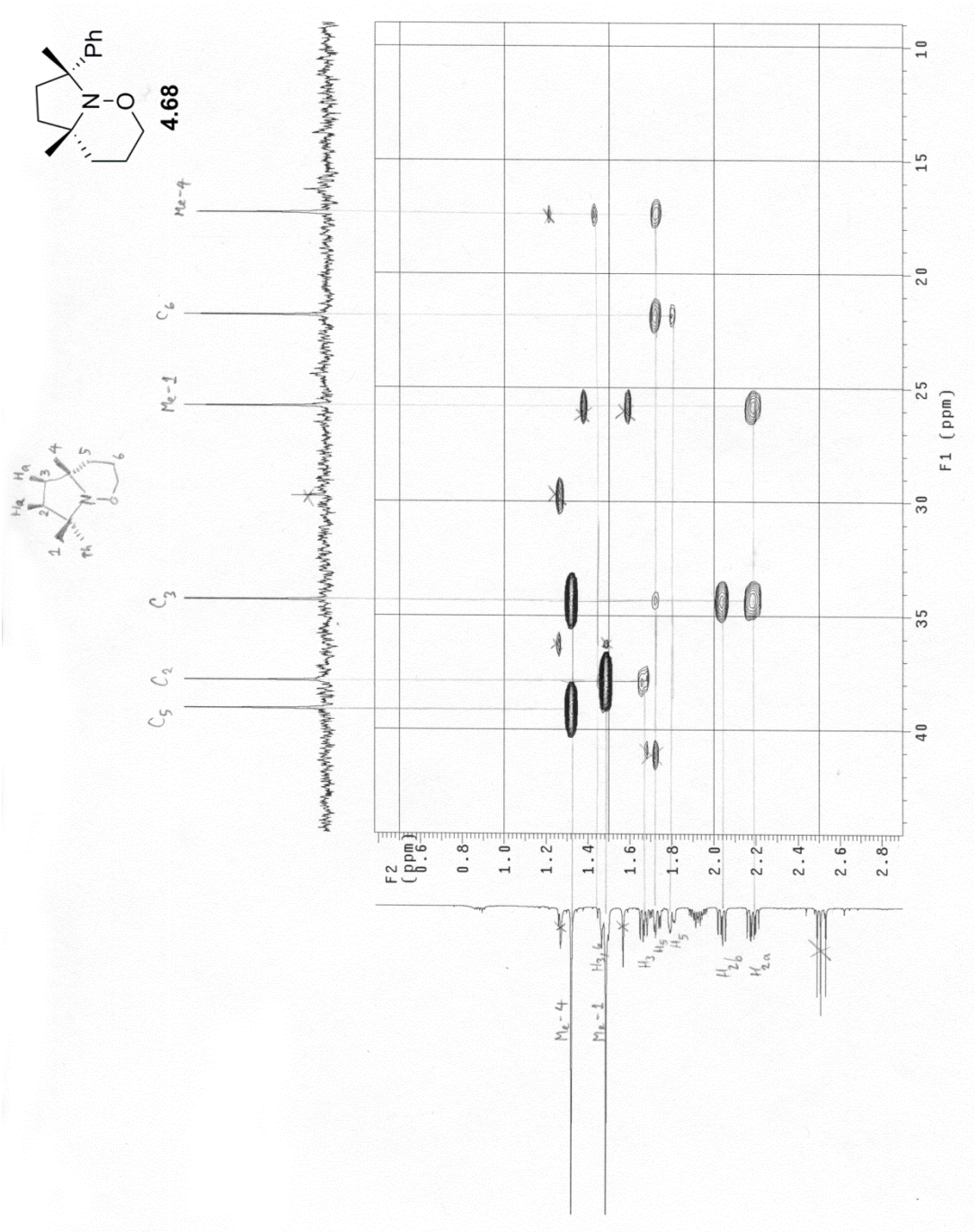
HMBC(1)



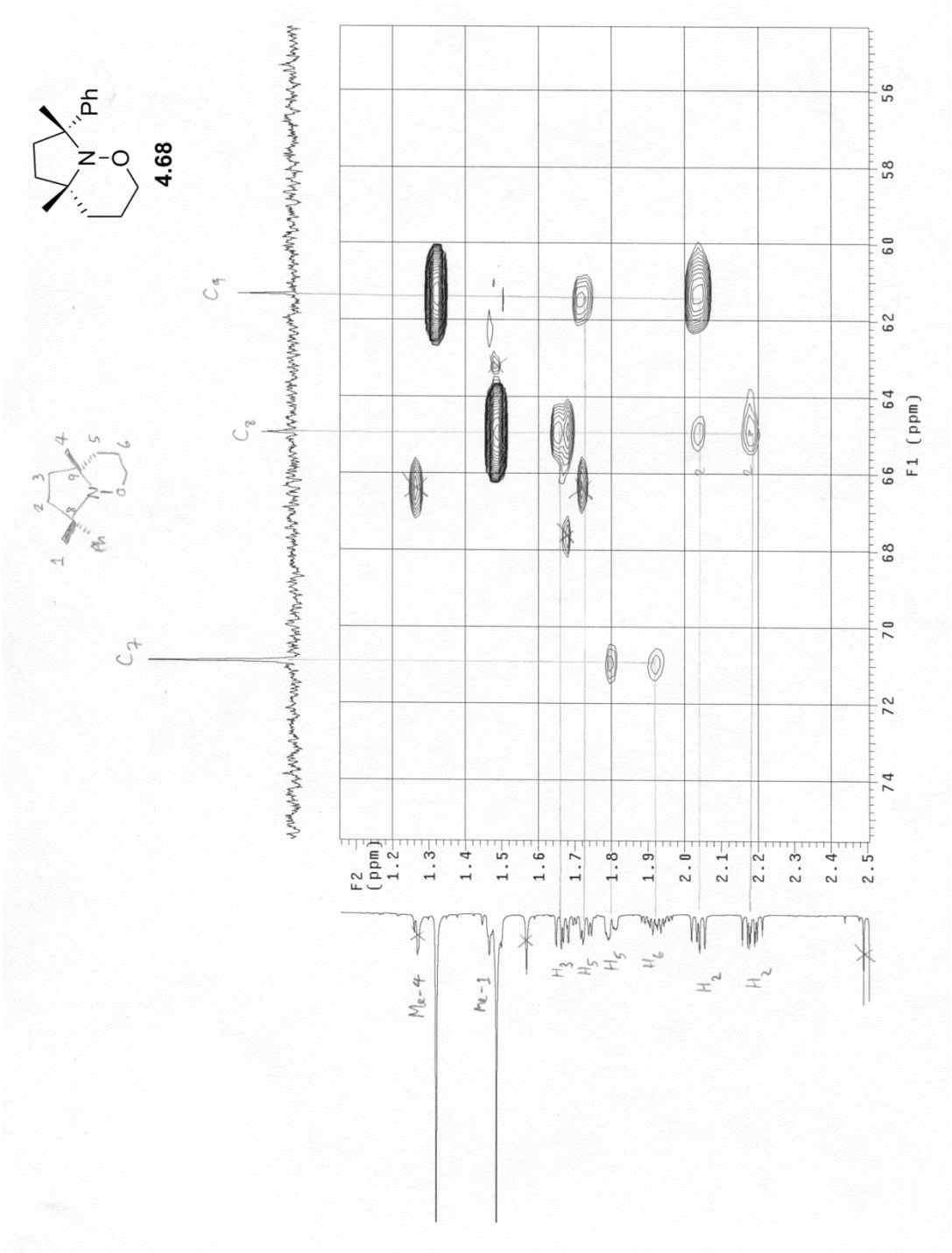
HMBC(2)



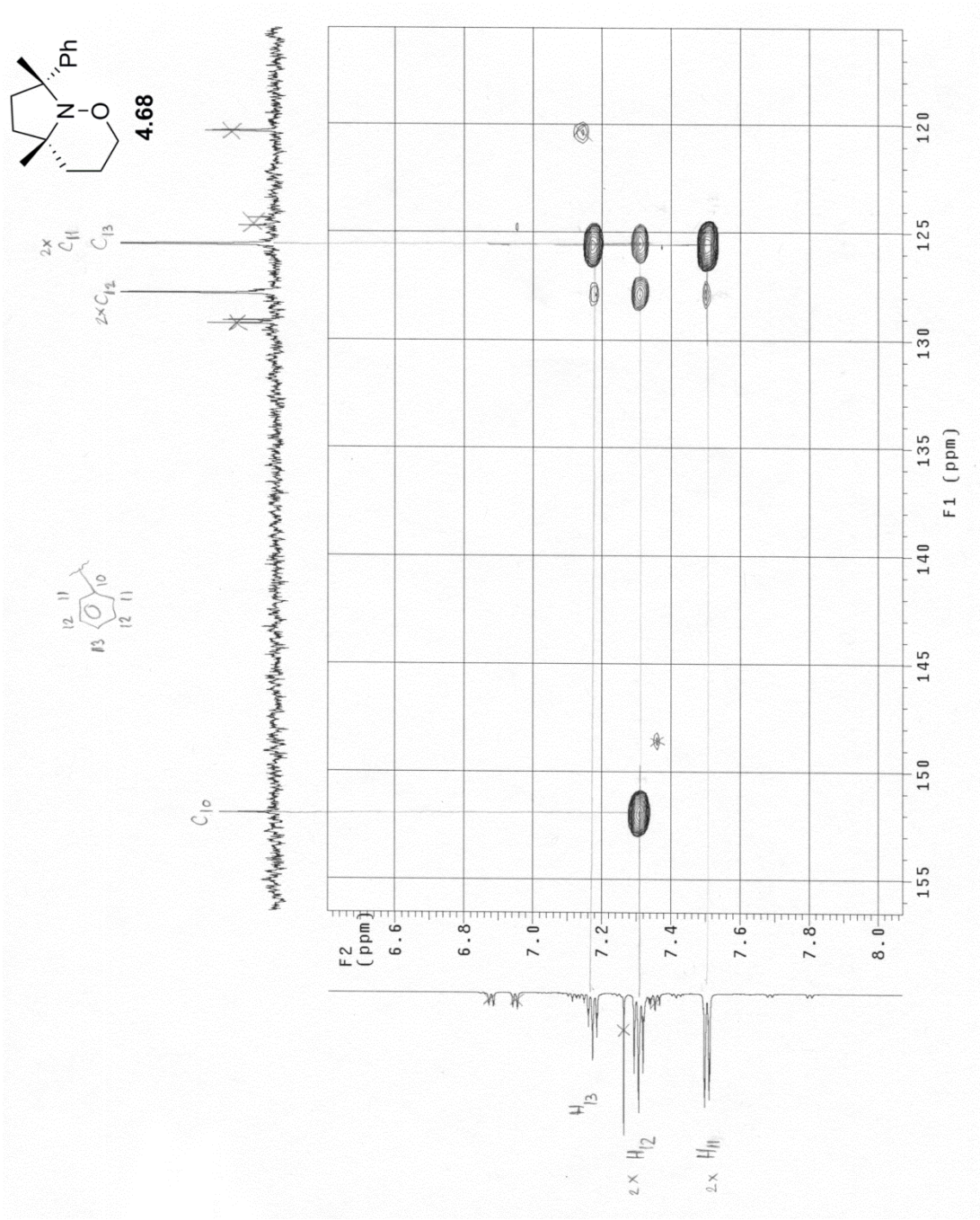
HMBC(3)



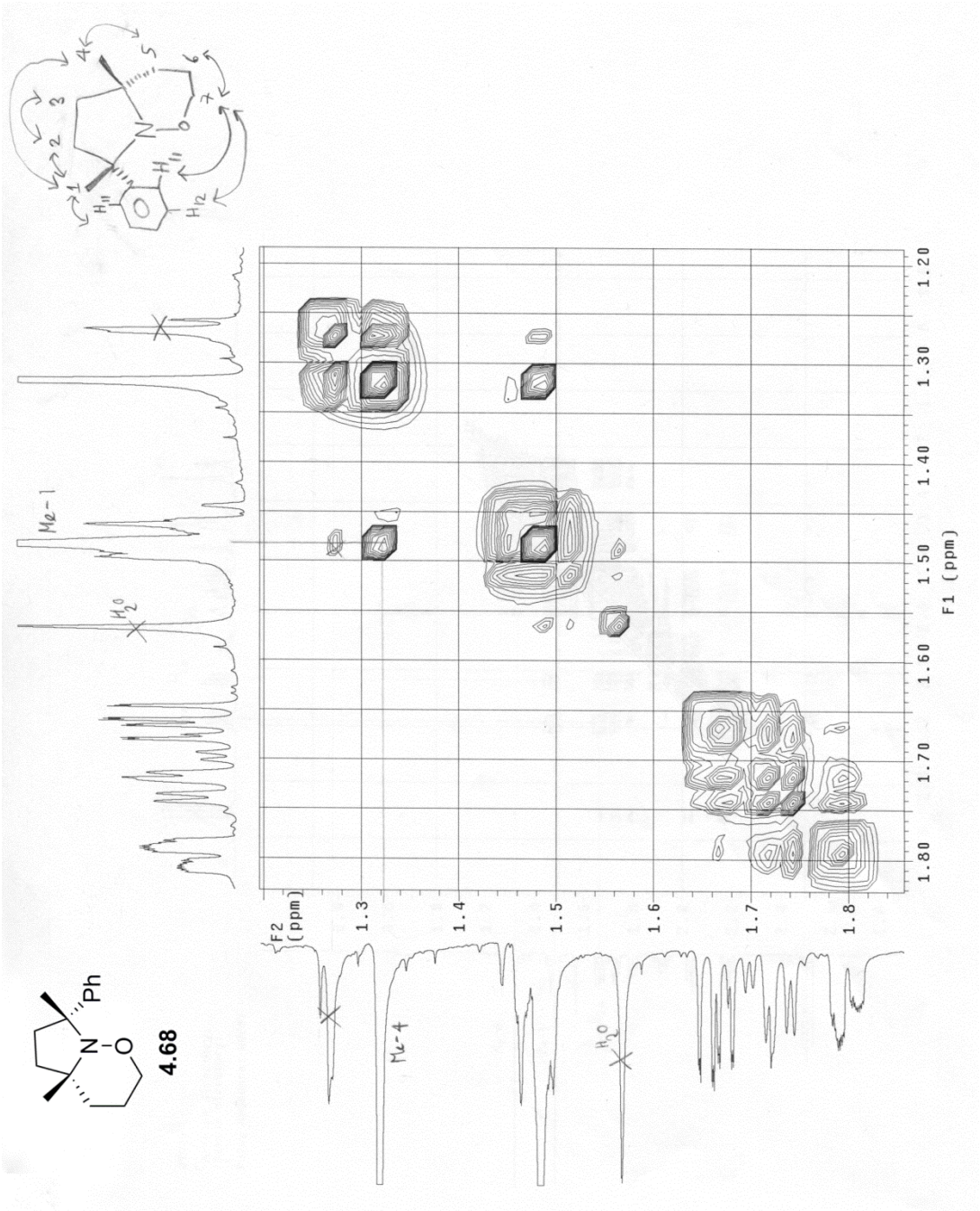
HMBC (4)

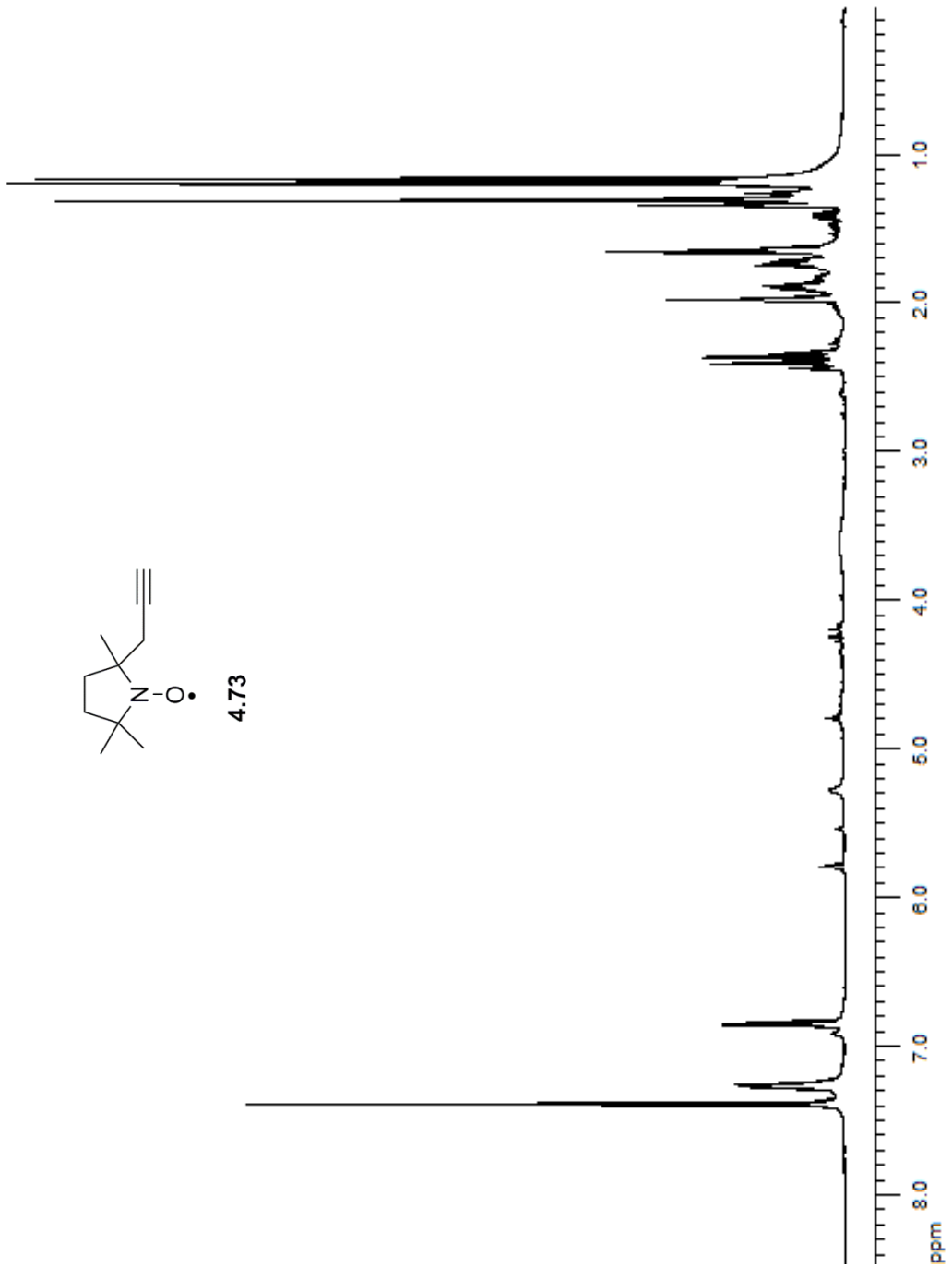


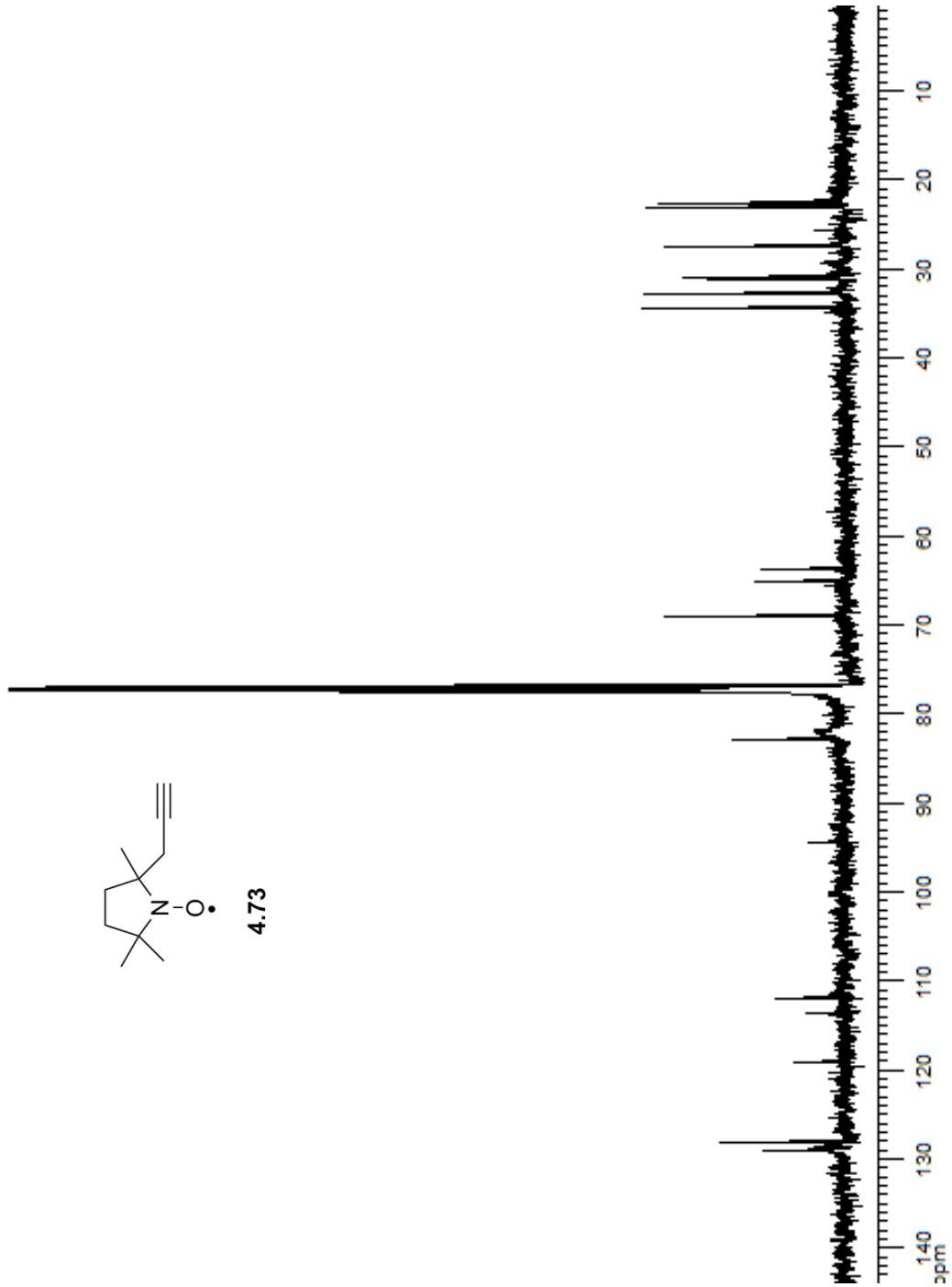
HMBC(5)


Ph
N
O
4.68
2x C11
C13
2x C12
C10
F2 (ppm)
6.6
6.8
7.0
7.2
7.4
7.6
7.8
8.0
155
150
145
140
135
130
125
120
F1 (ppm)
H13
2x H12
2x H11

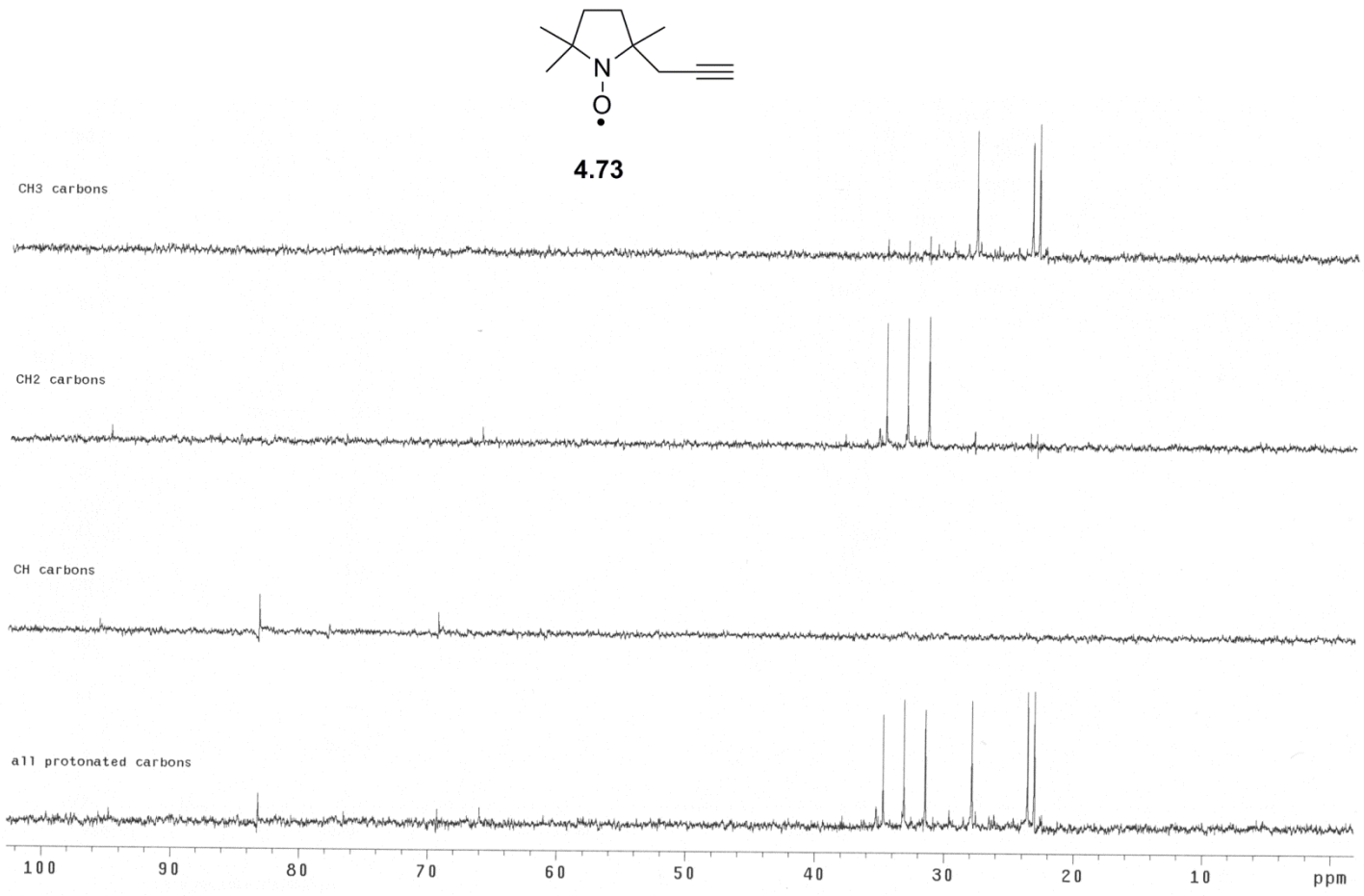
NOESY


Me-1
H2O
Me-4
H2O
F2 (ppm)
F1 (ppm)
1.3
1.4
1.5
1.6
1.7
1.8
1.20
1.30
1.40
1.50
1.60
1.70
1.80
Ph
N
O
4.68

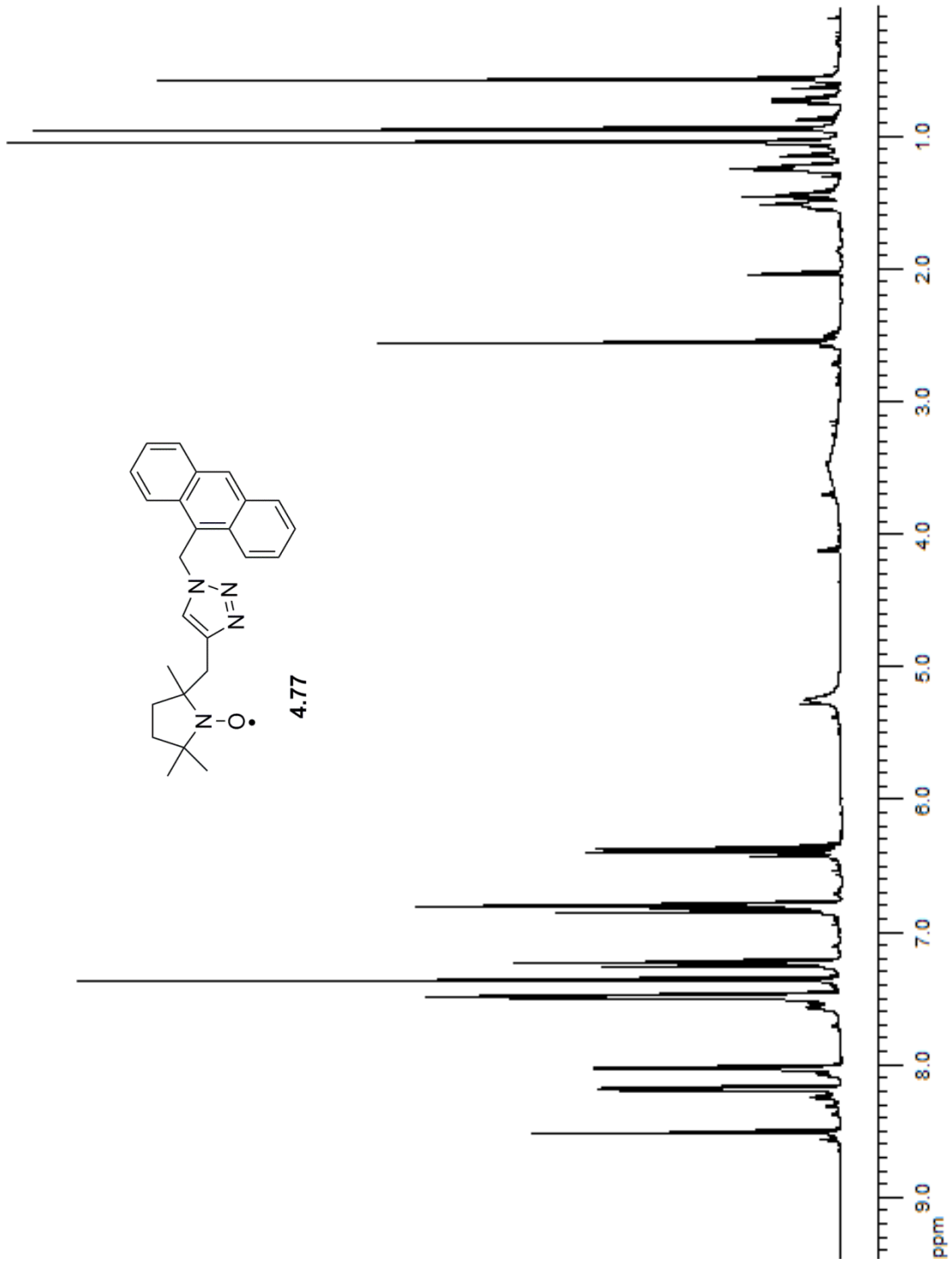

4.73
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

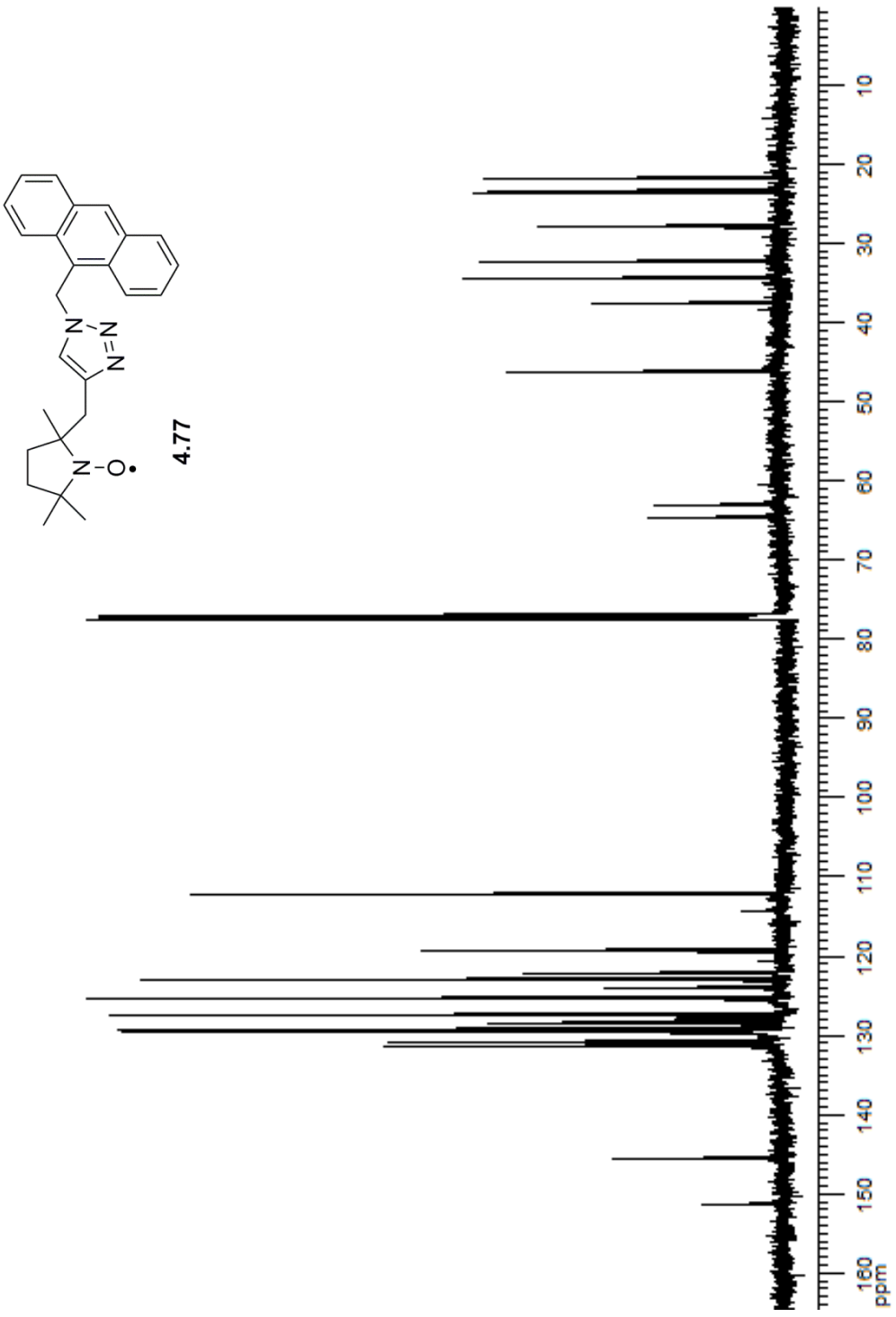


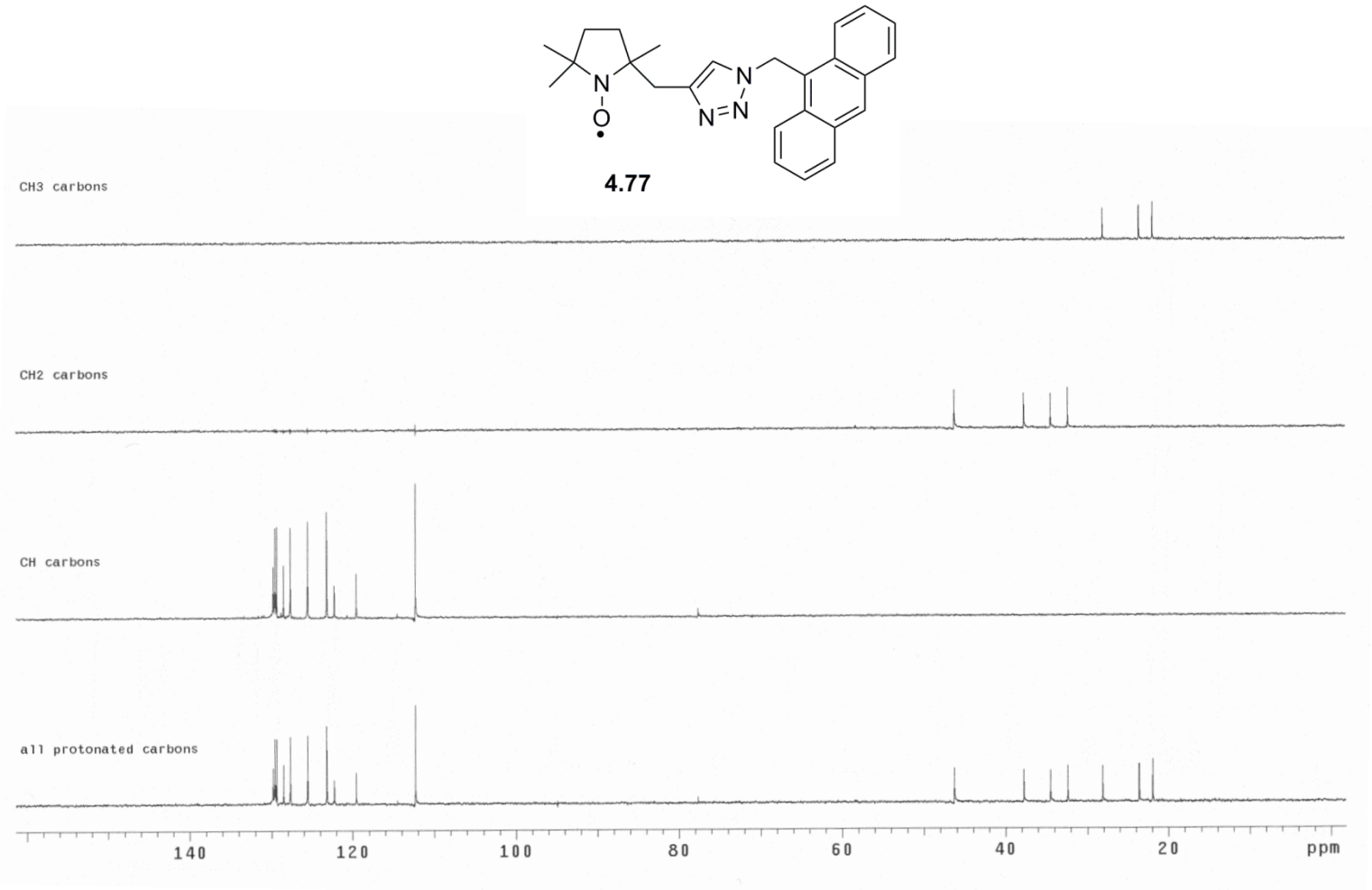
4.73

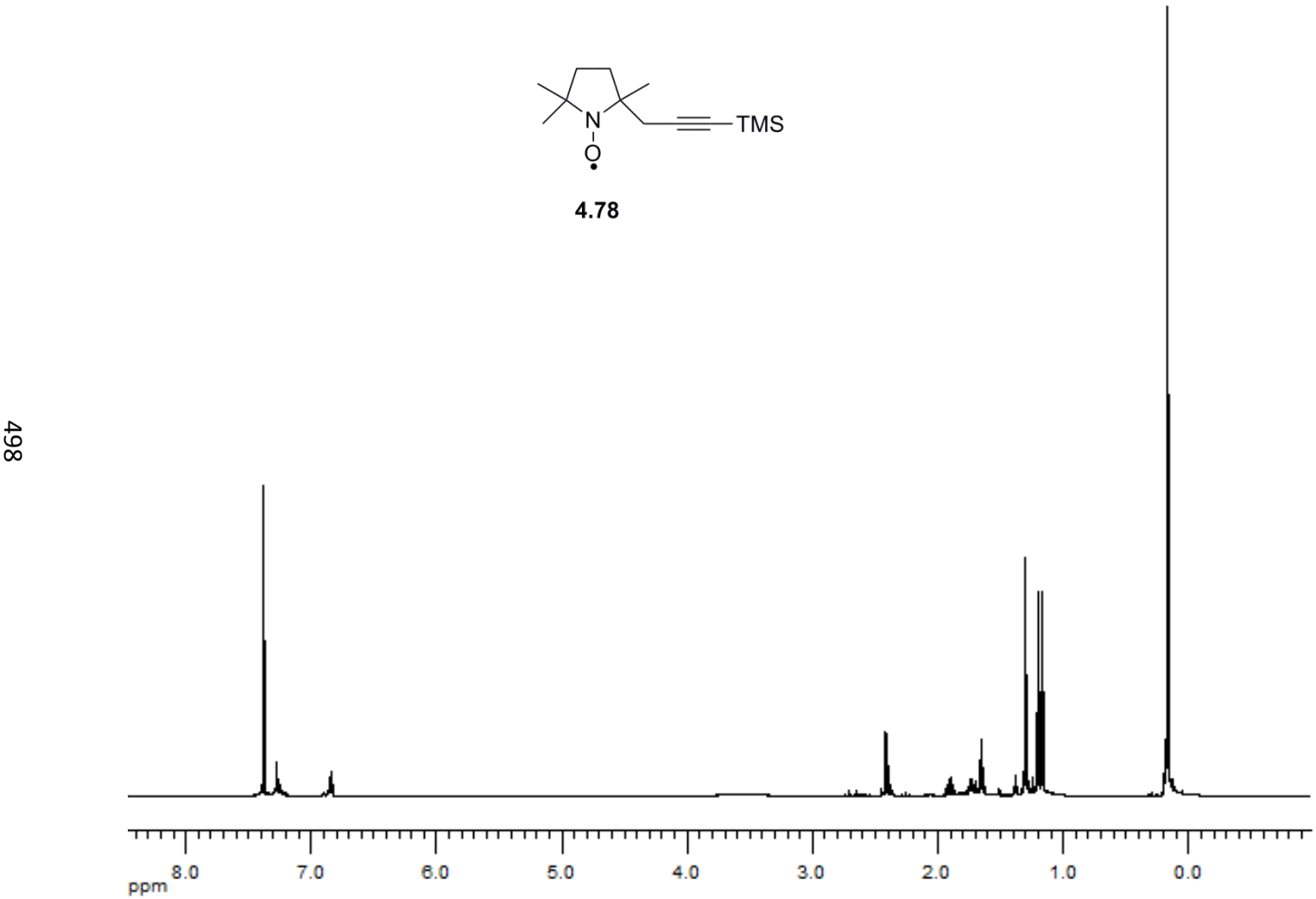

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
100
90
80
70
60
50
40
30
20
10
ppm

4.73

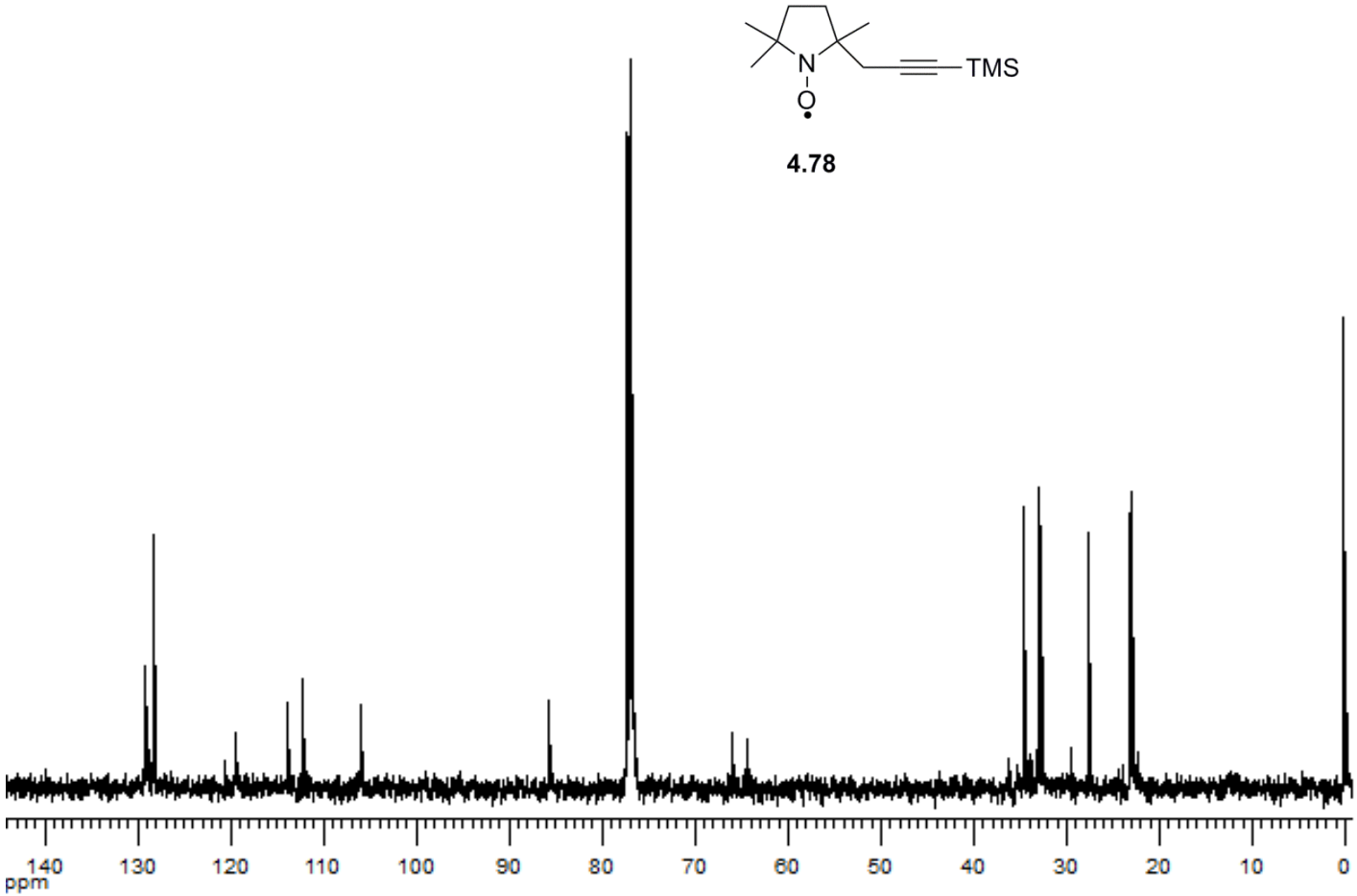

4.77
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm


4.77
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm

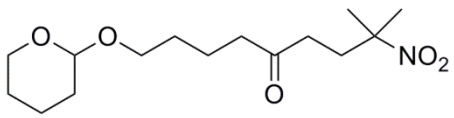

4.77
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
140
120
100
80
60
40
20
ppm



4.78

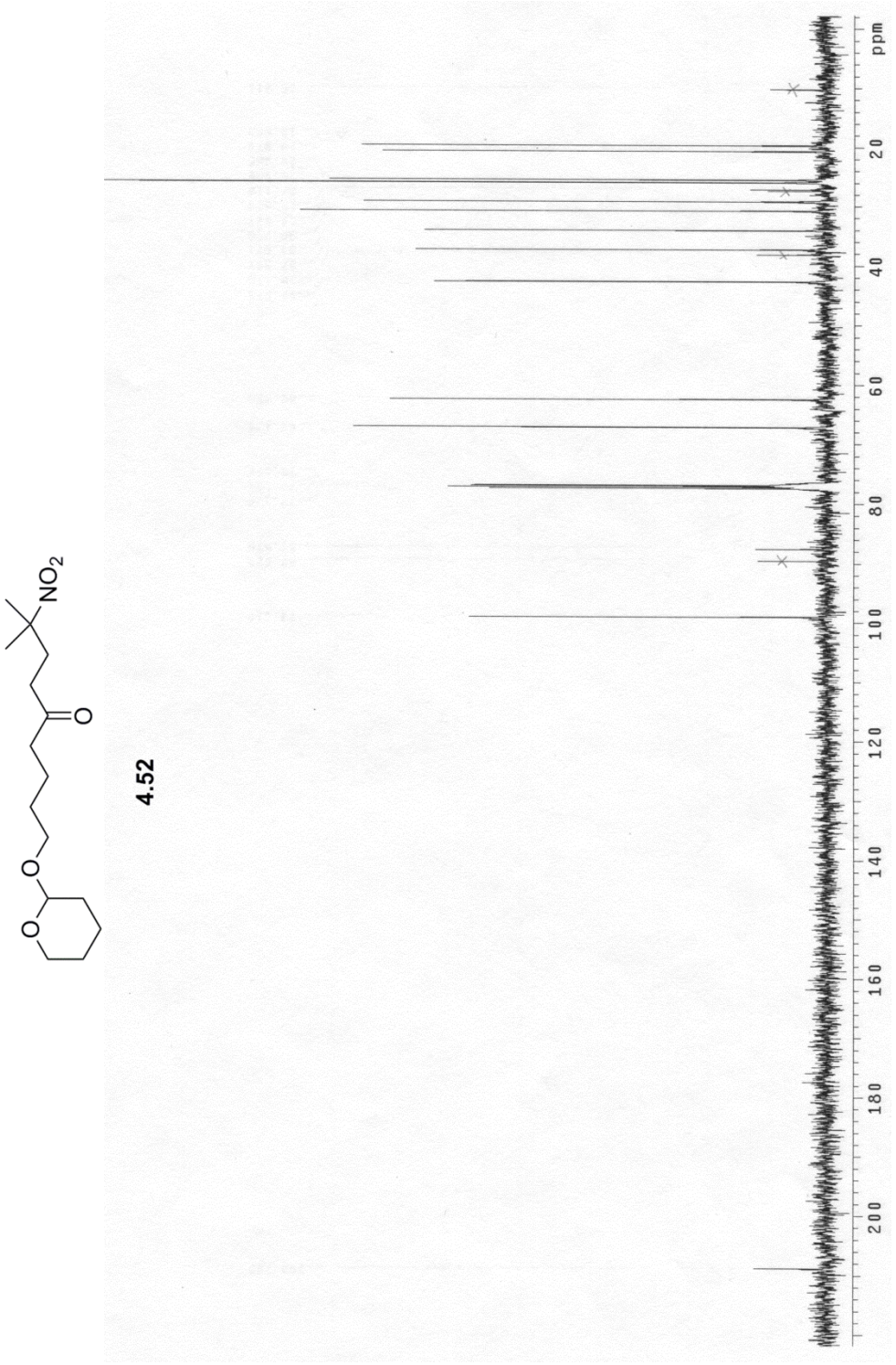


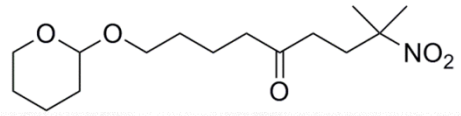
4.78



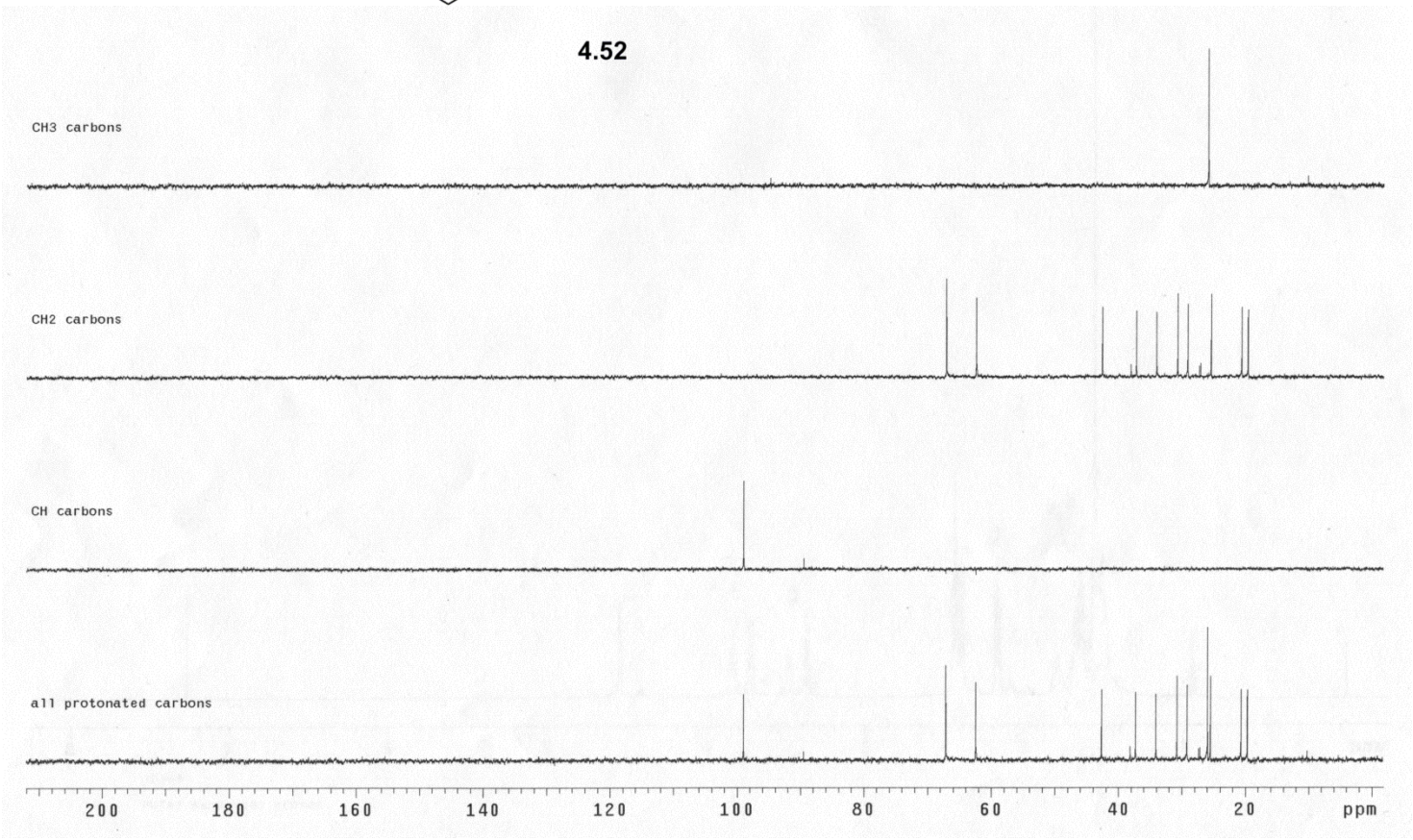
4.52

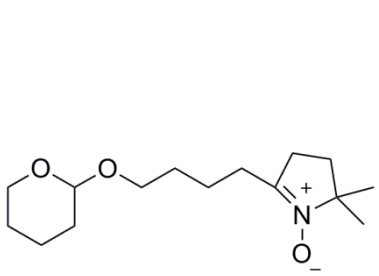
500


NO2
O
O
O
4.52
ppm
200
180
160
140
120
100
80
60
40
20


O
O
O
NO2

4.52


CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
ppm



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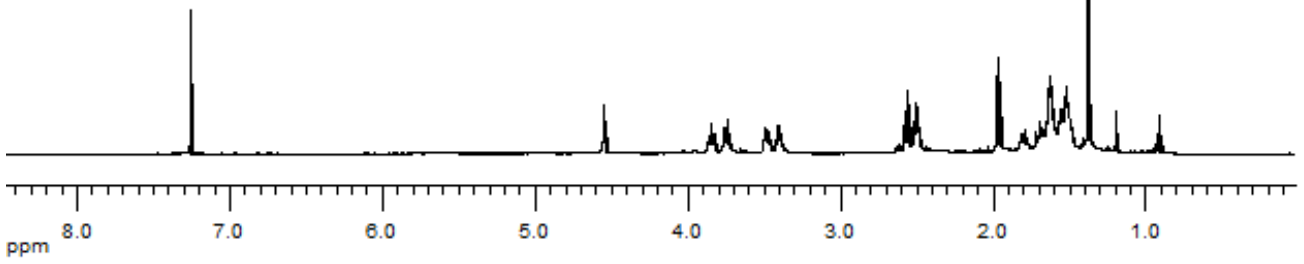

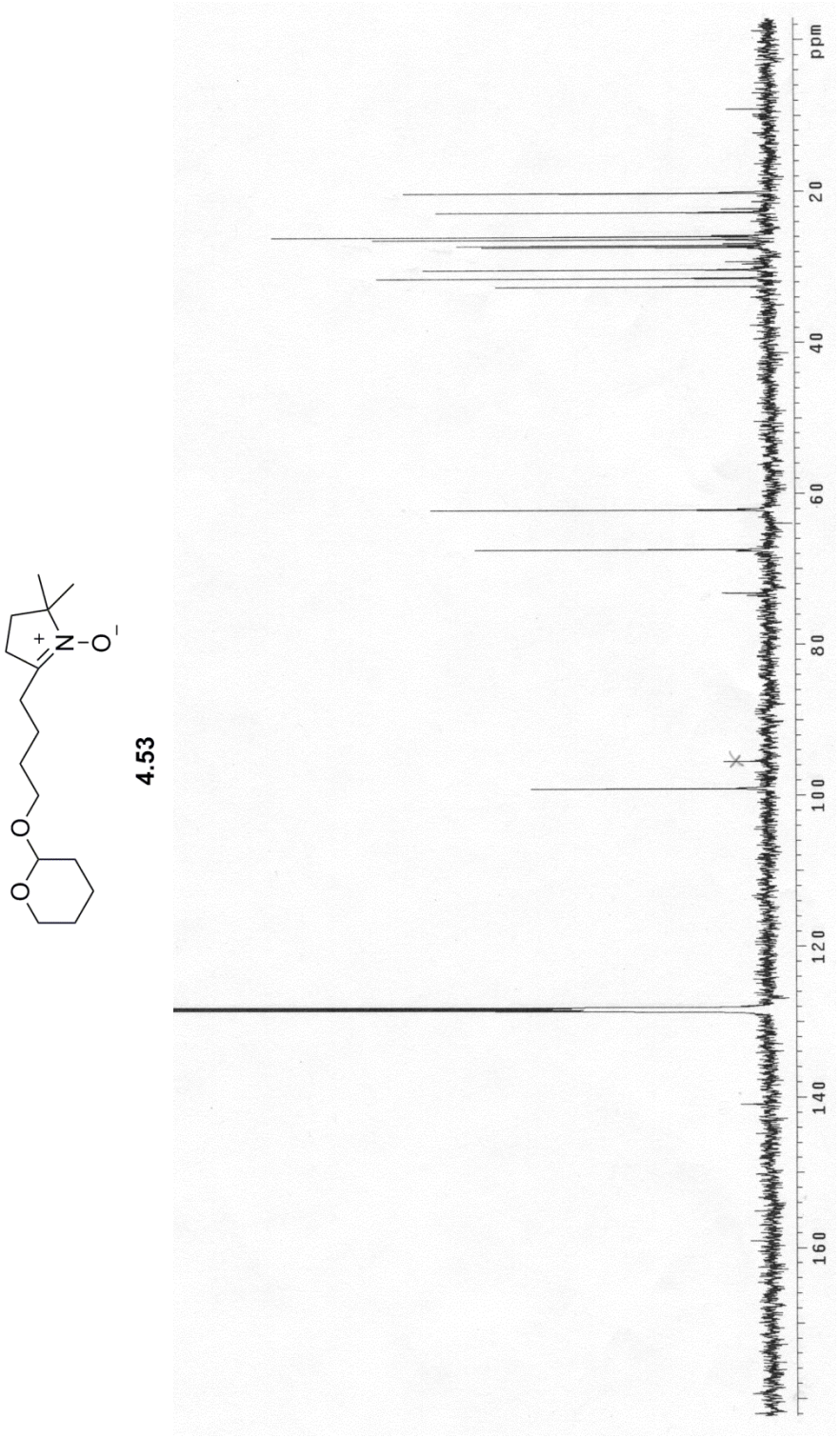

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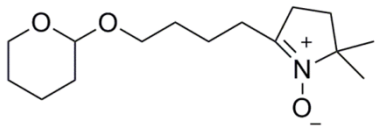

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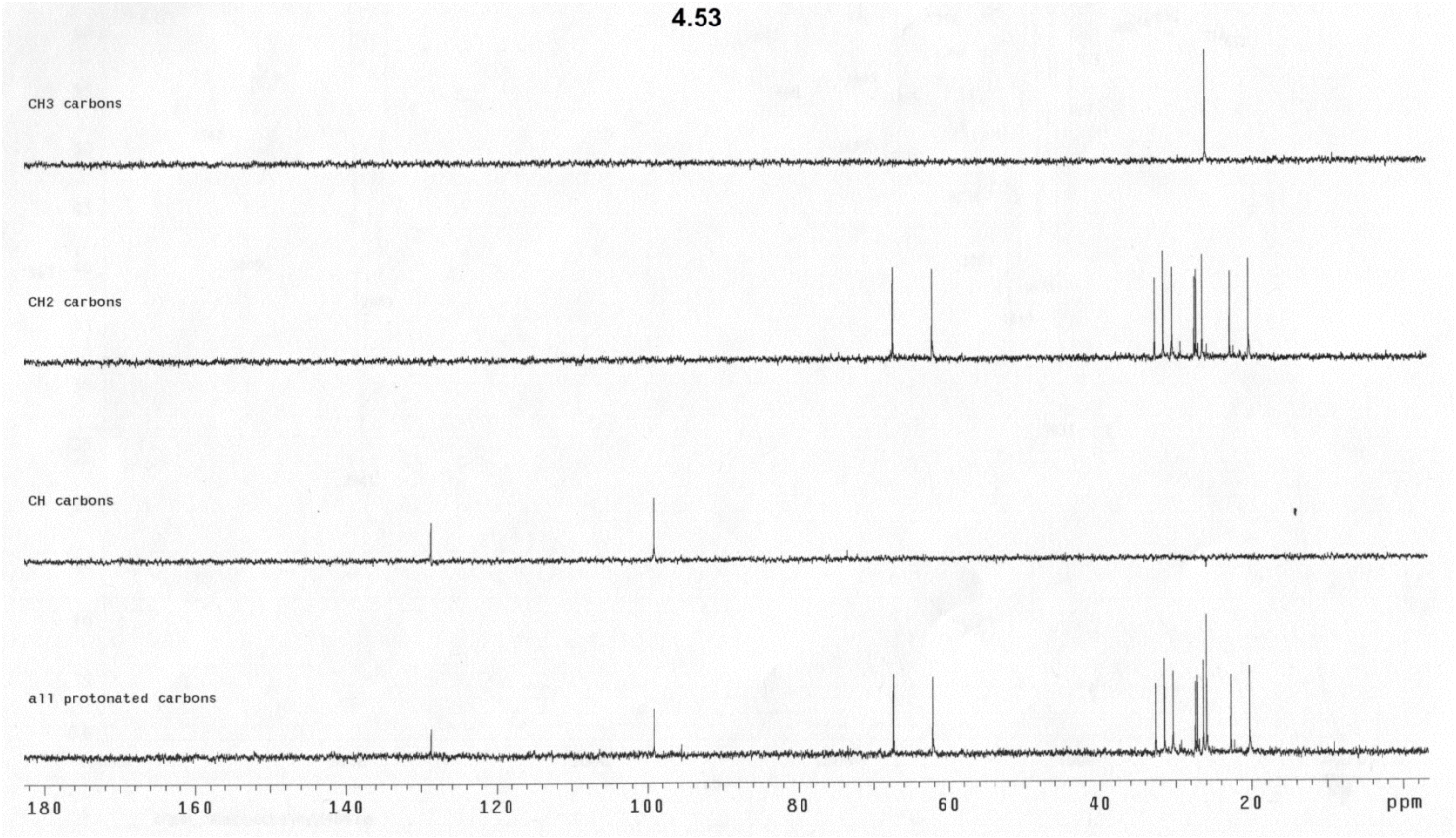
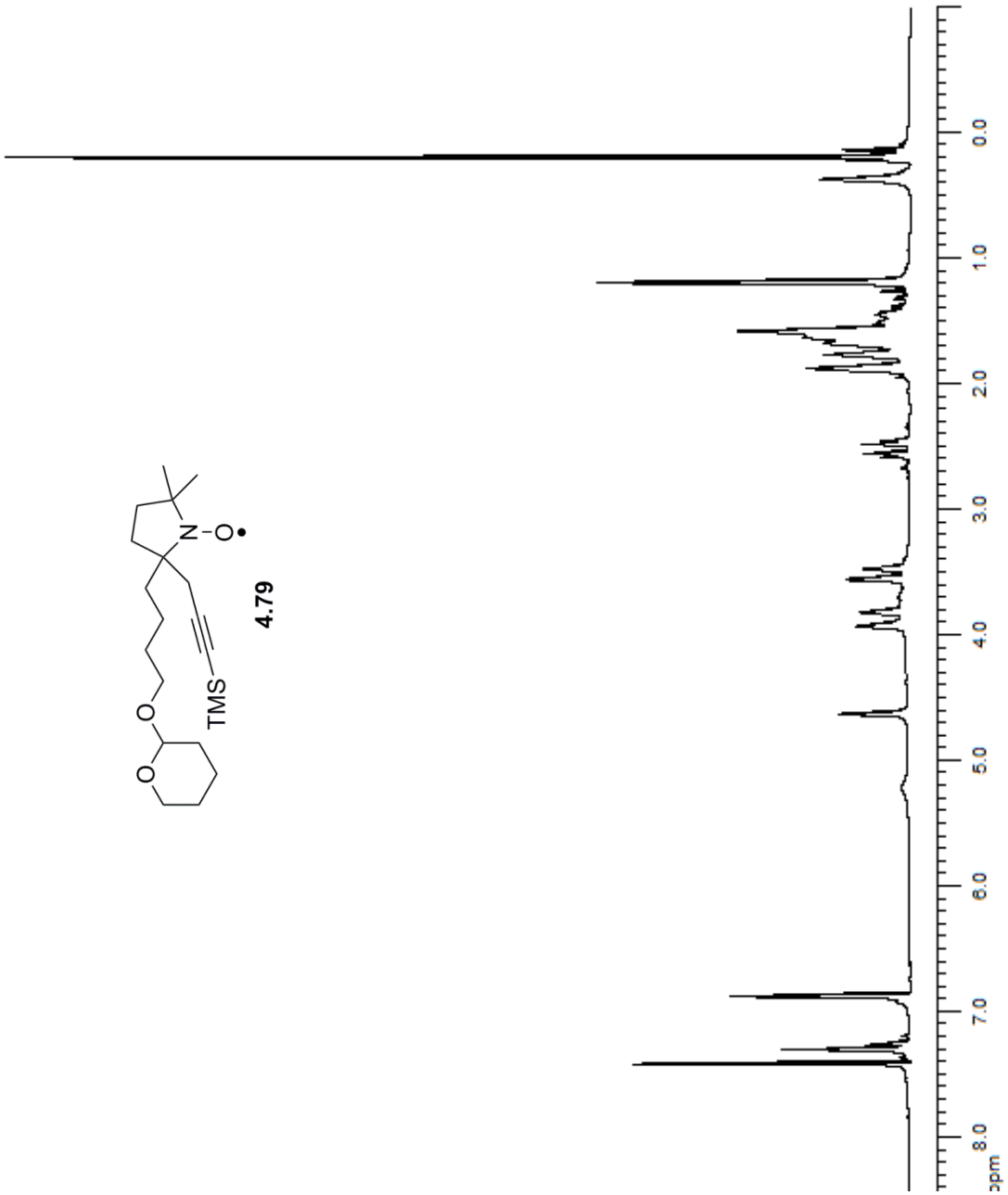
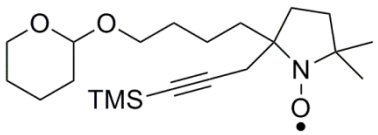
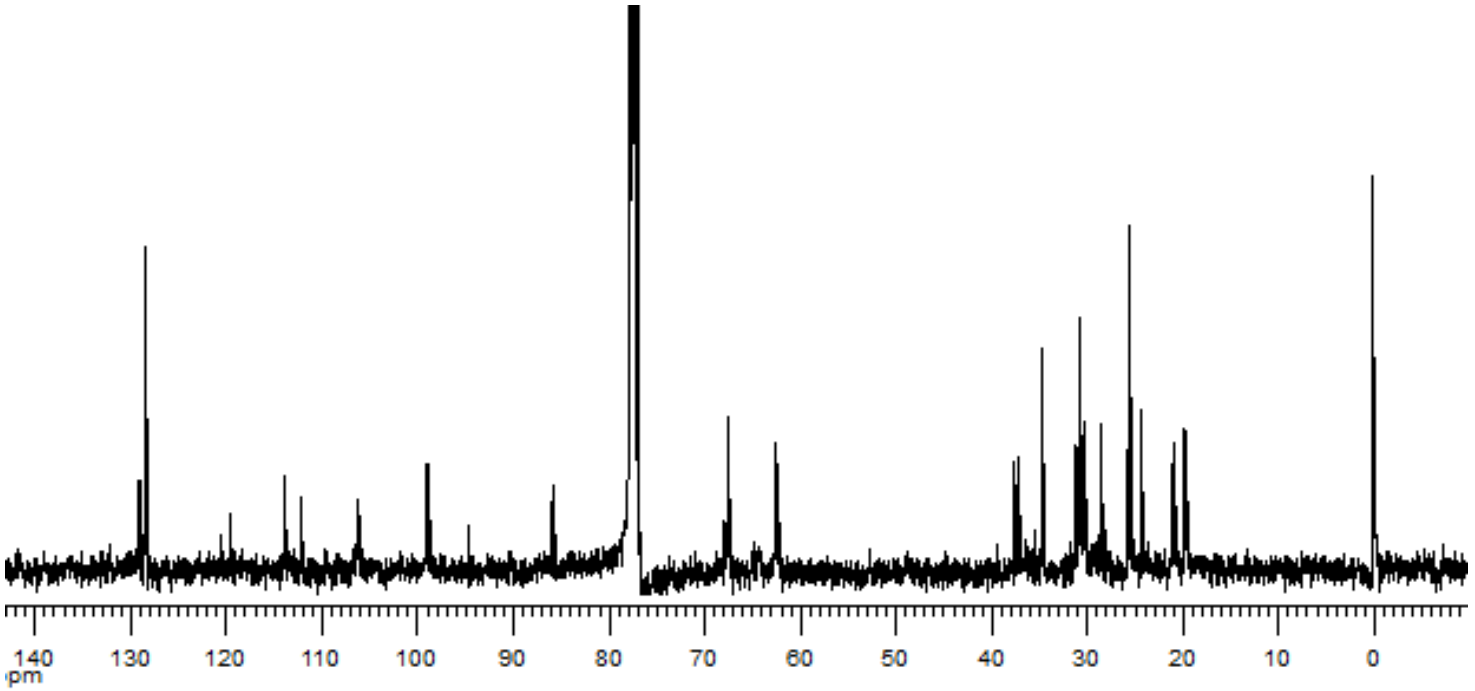
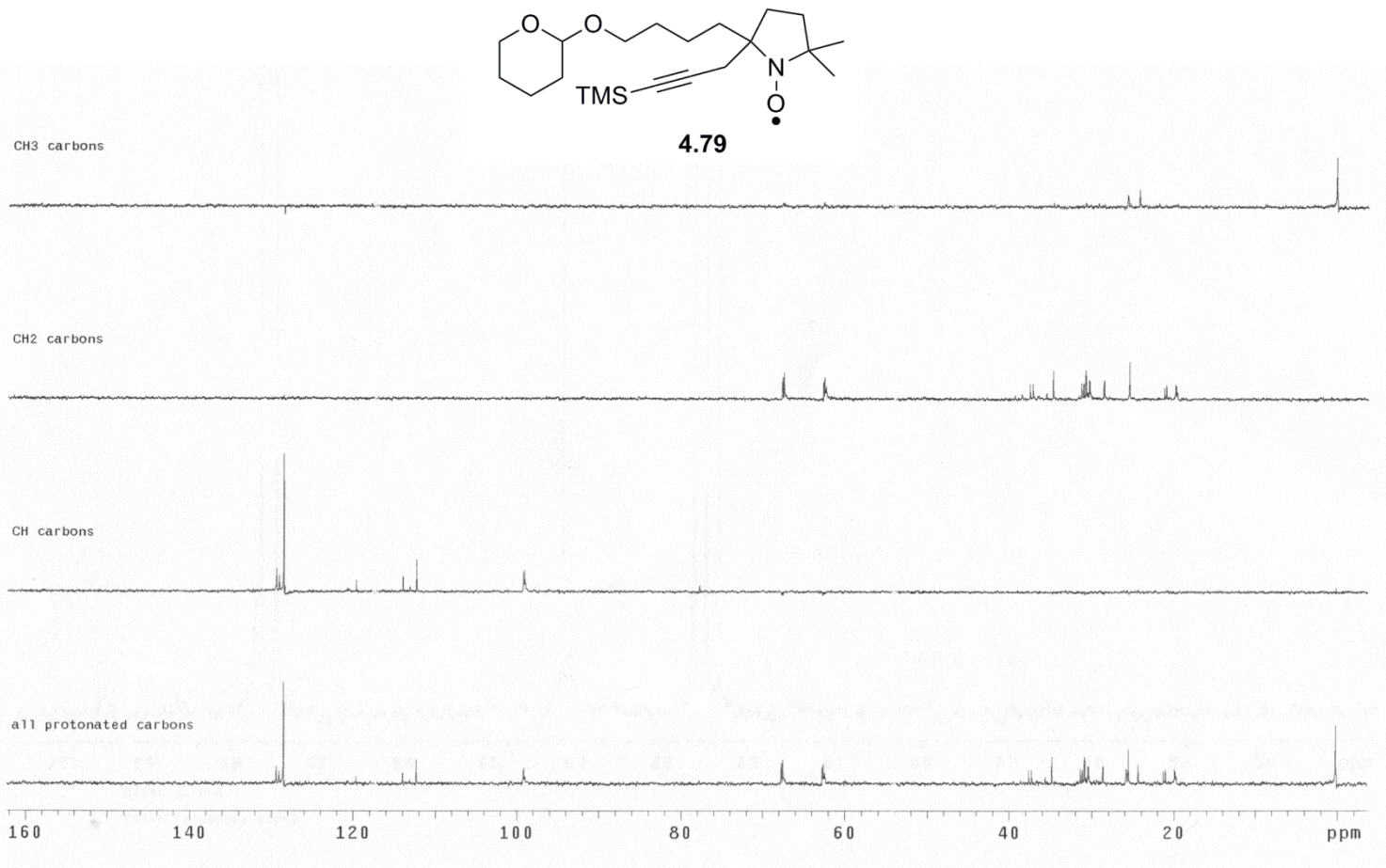

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm

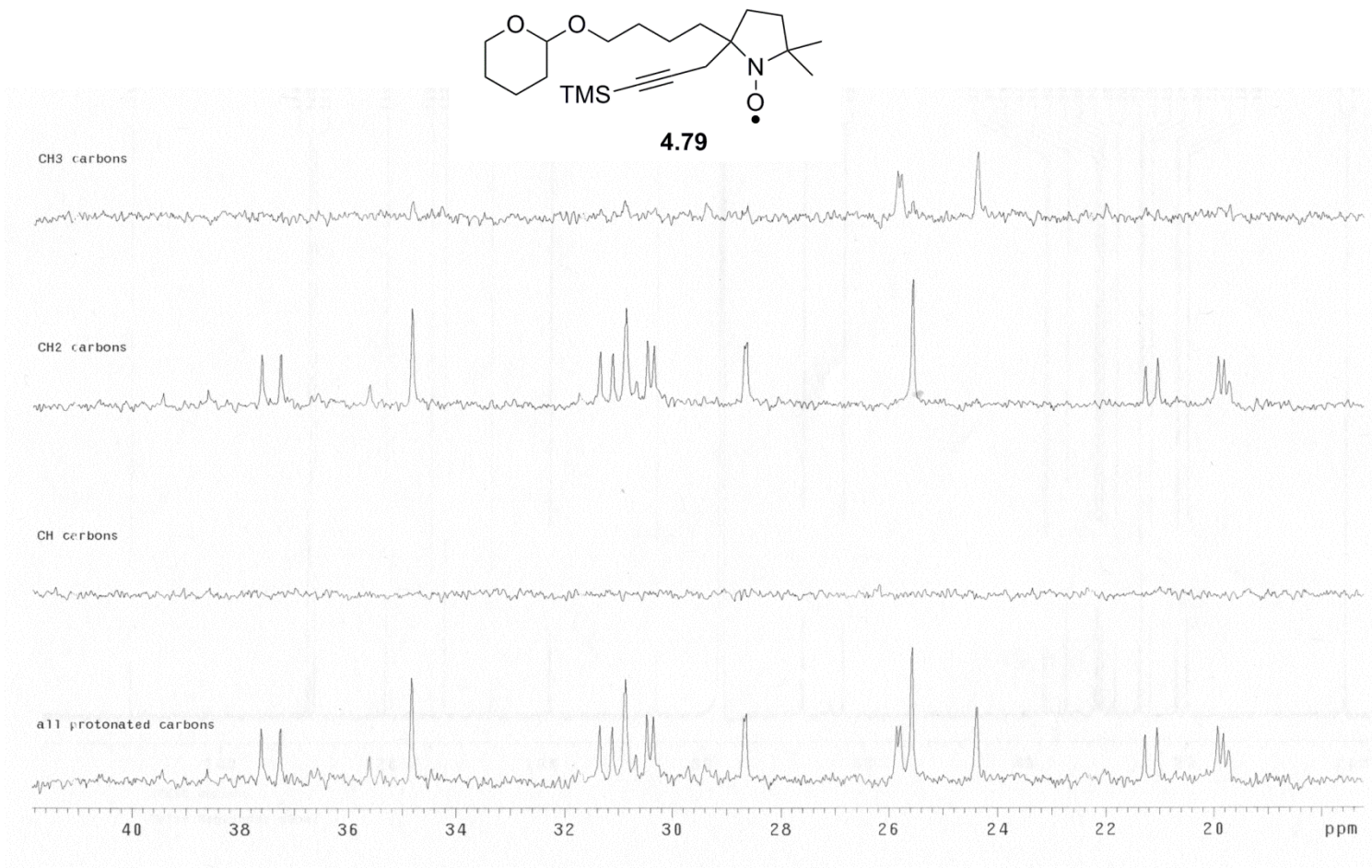

N
O
TMS
O
O
4.79
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm

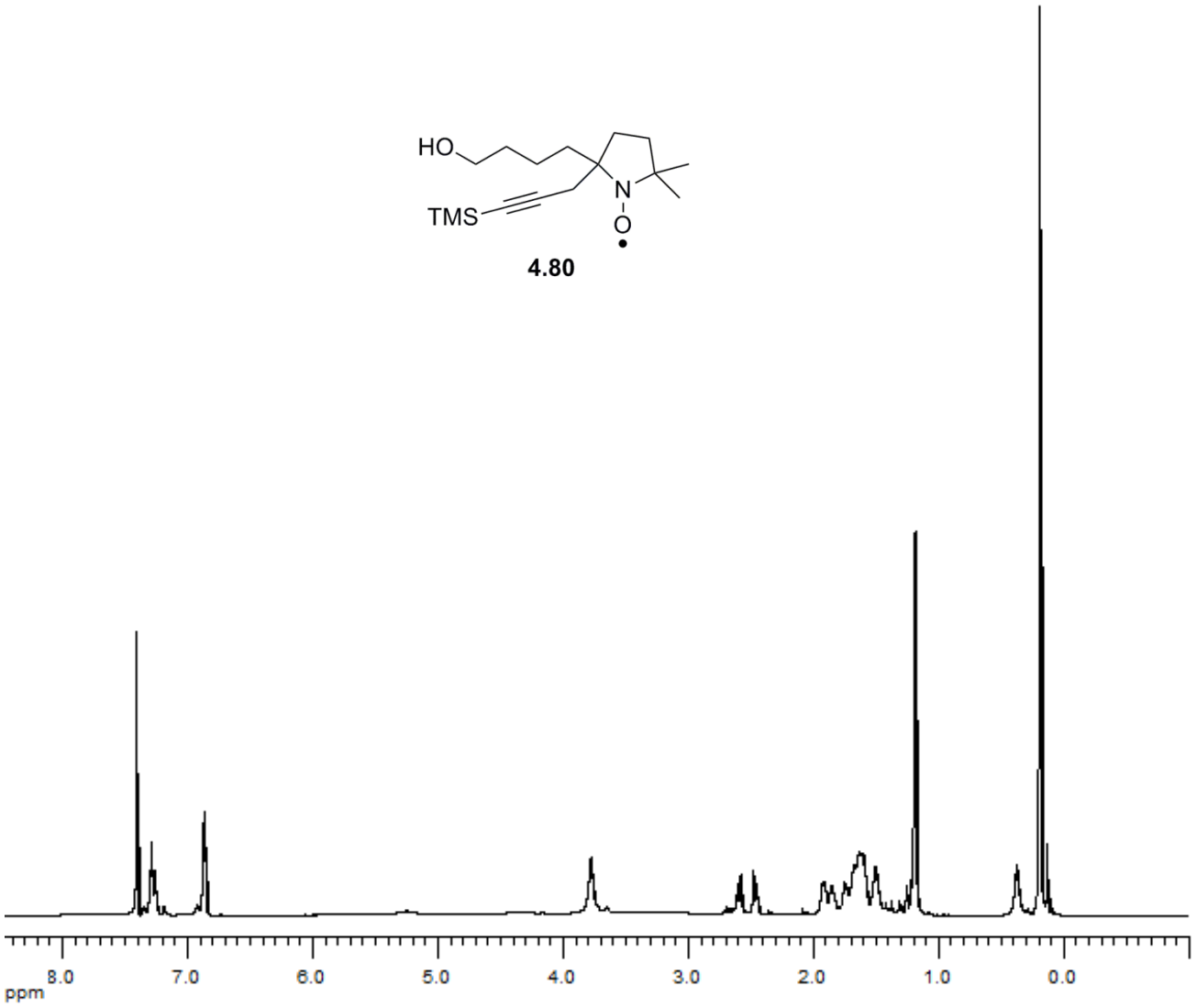


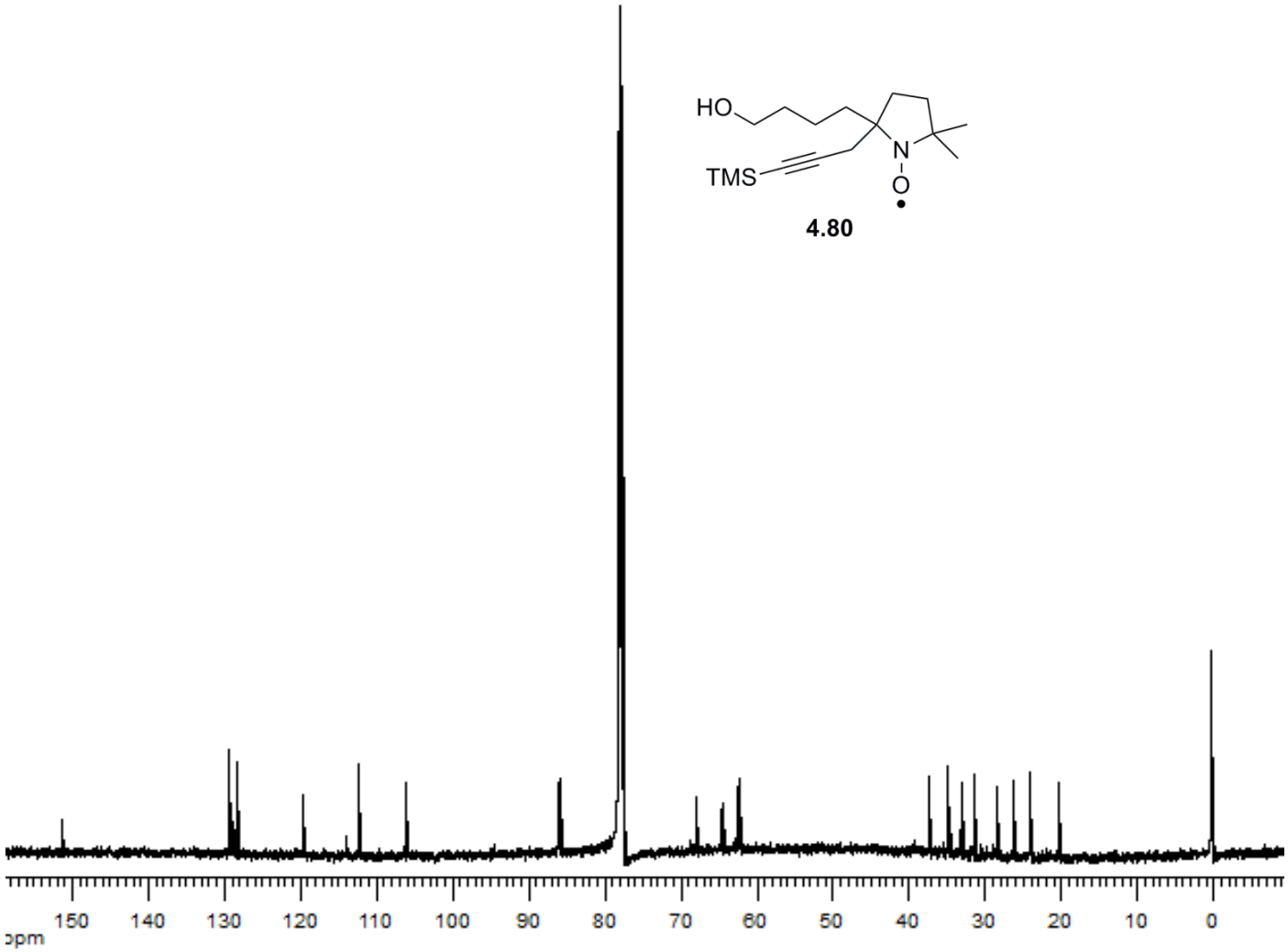
4.79

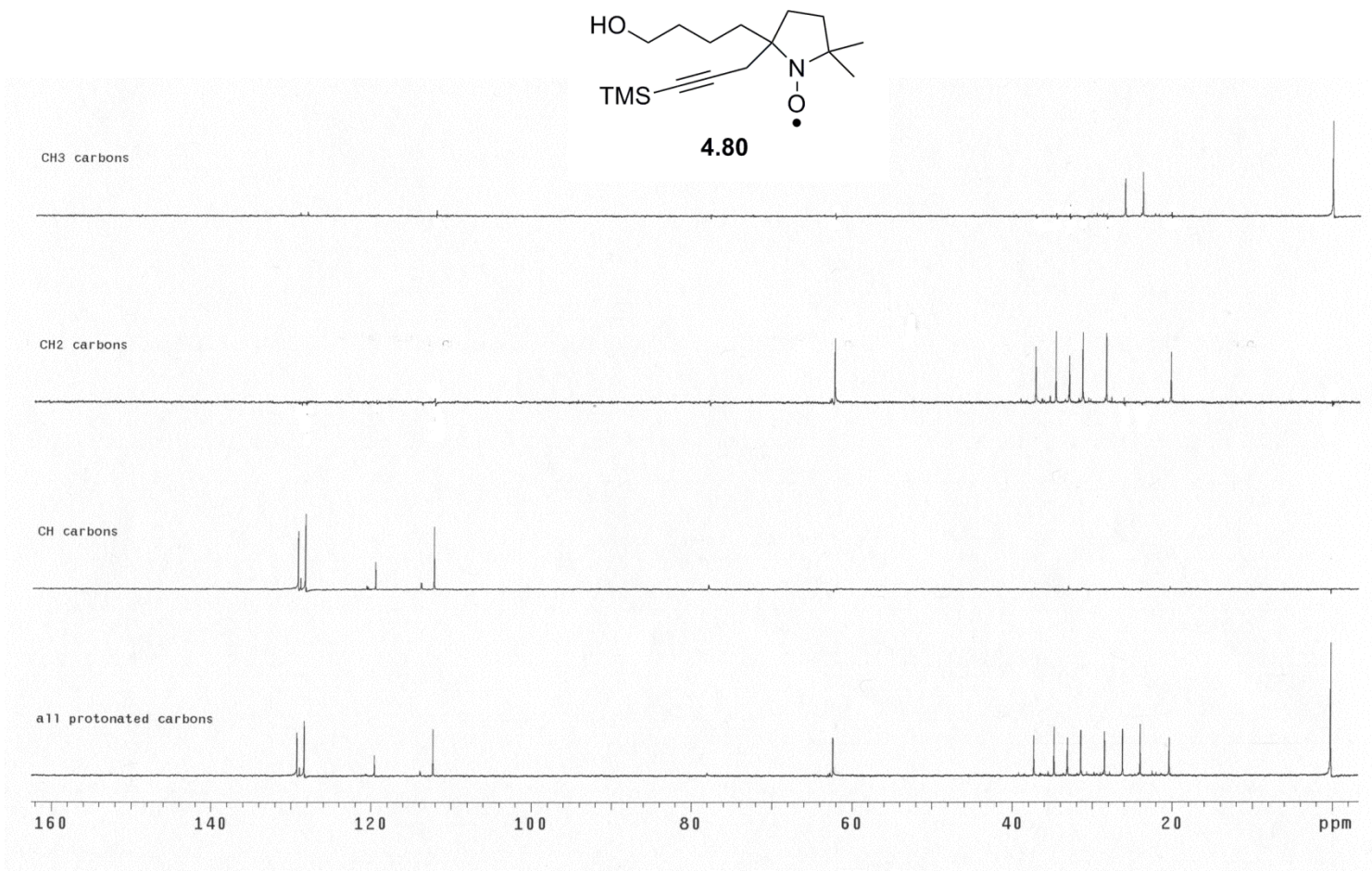


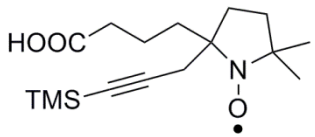

TMS
4.79
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm


TMS
4.79
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
40
38
36
34
32
30
28
26
24
22
20
ppm

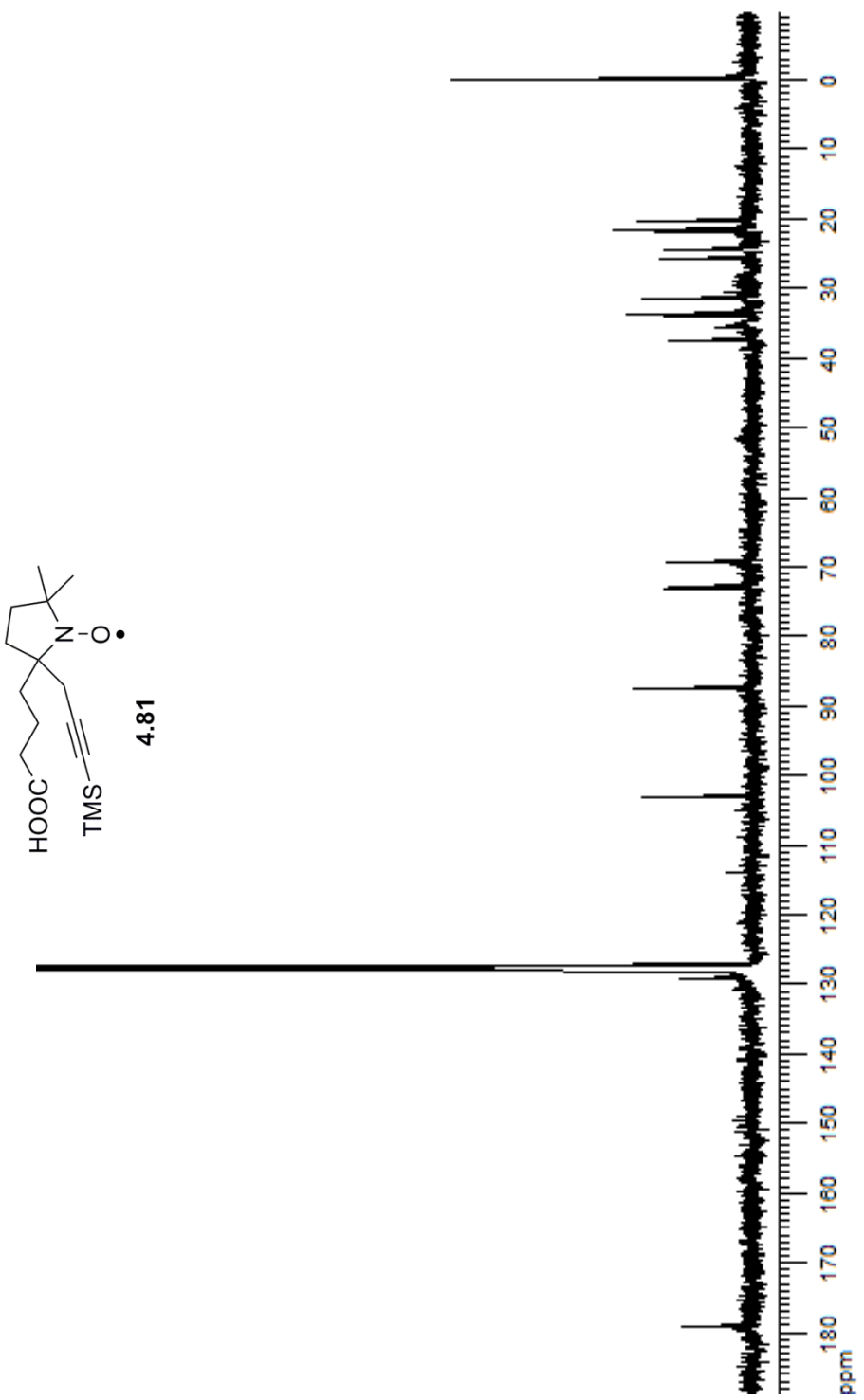

HO
TMS
N
O
4.80
ppm
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

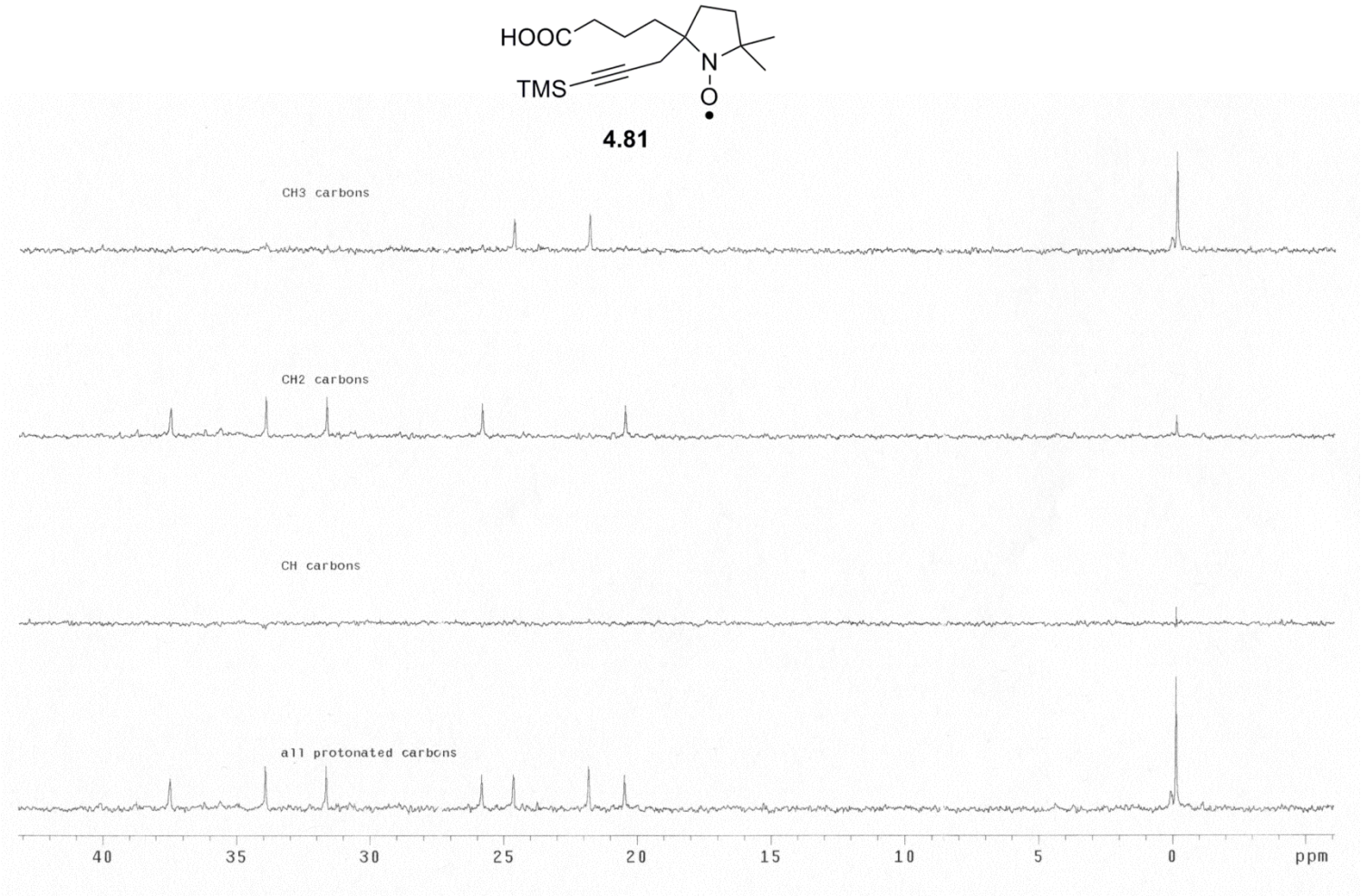

HO
TMS
N
O
4.80
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


HO
TMS
N
O
4.80
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm

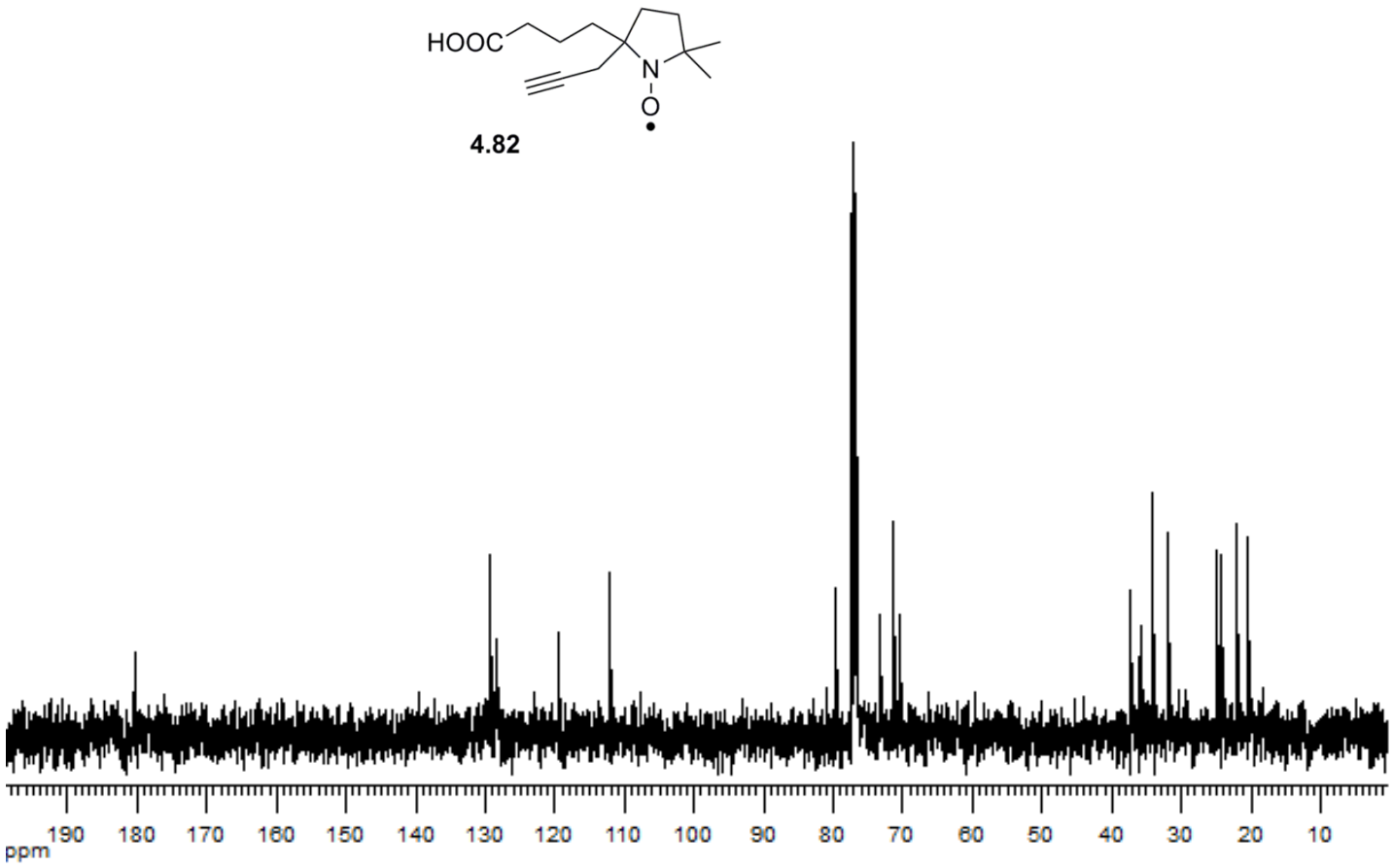


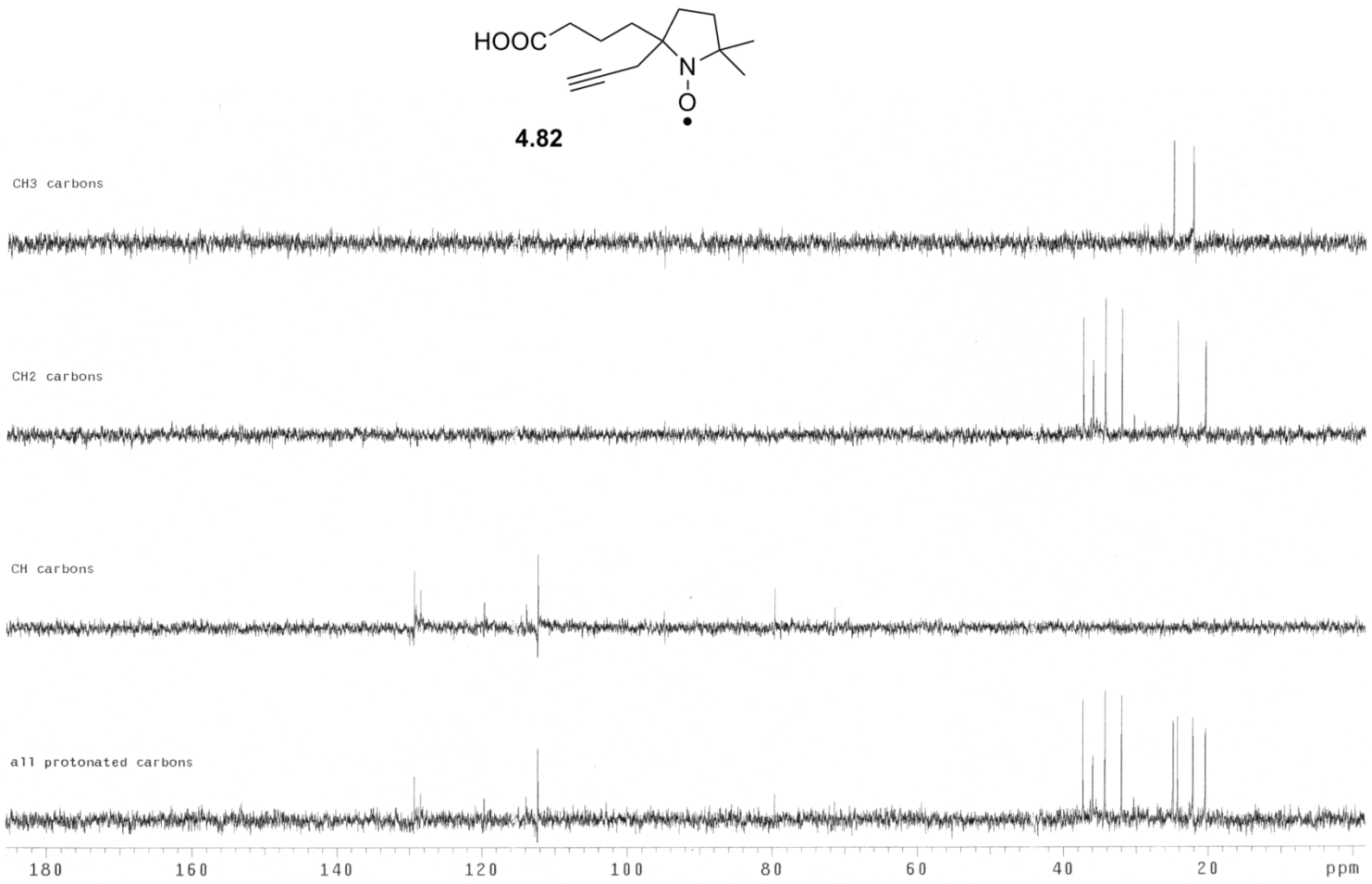
4.81

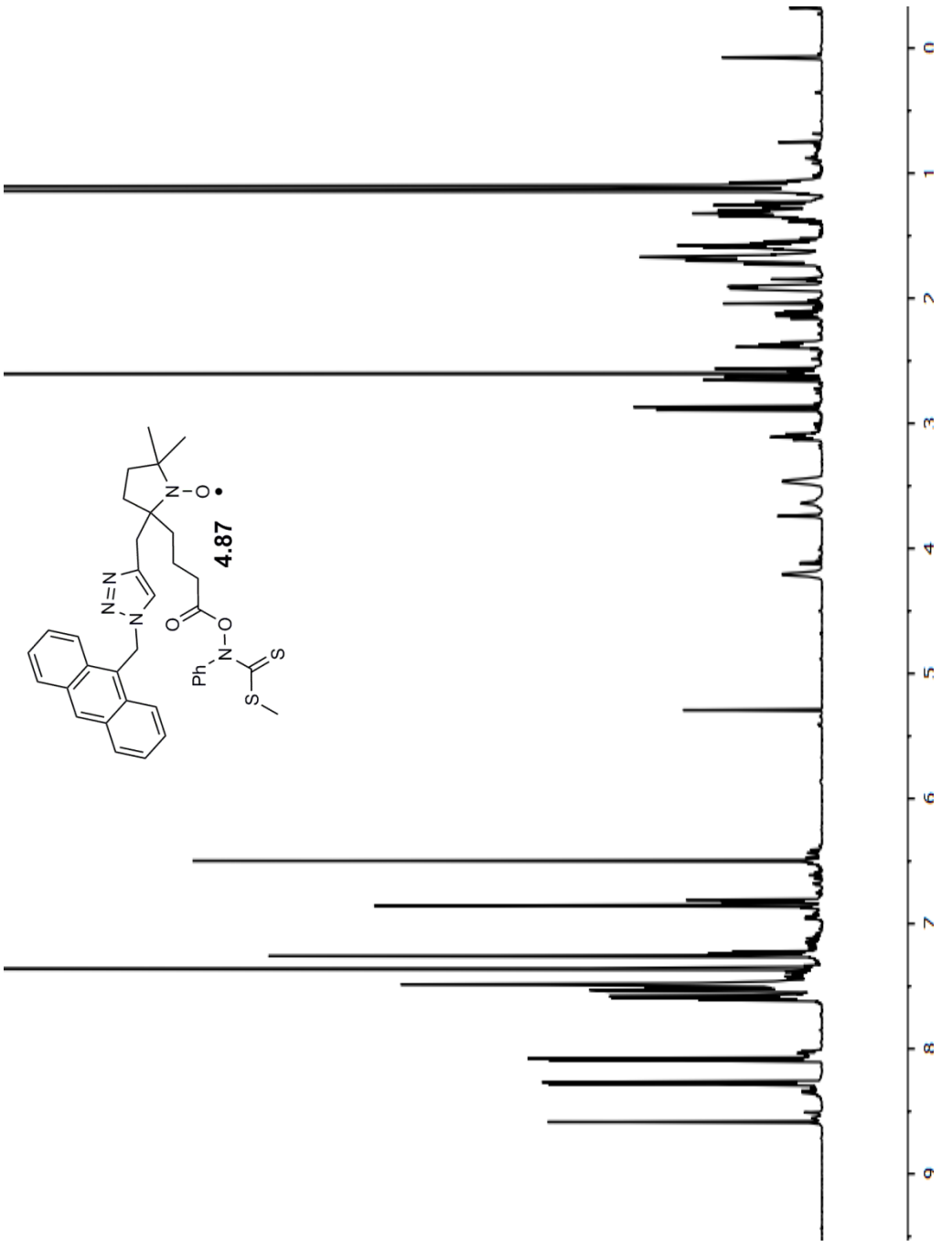

HOOC
TMS
N
O
4.81
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
ppm

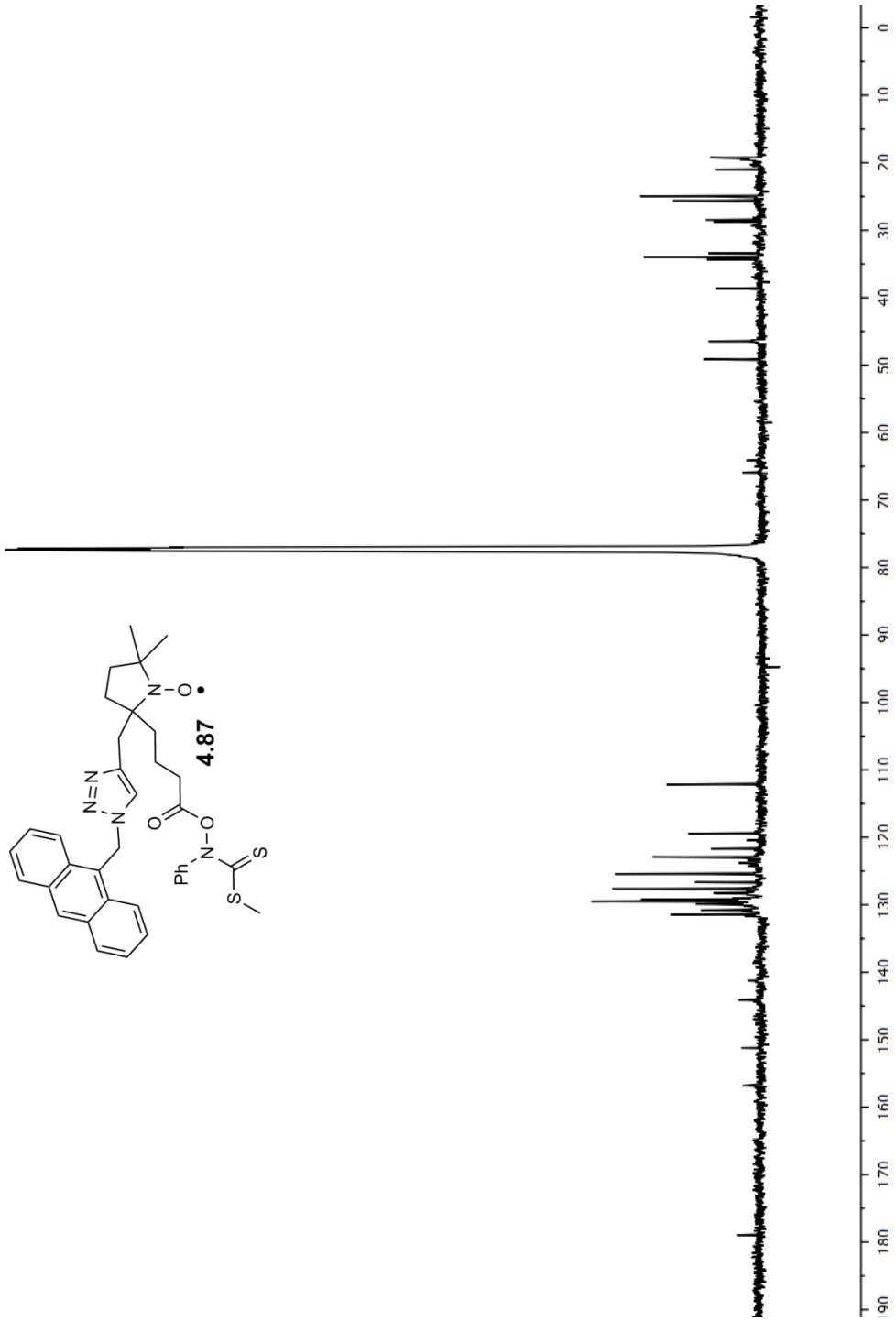

HOOC
TMS
N
O
4.81
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
40
35
30
25
20
15
10
5
0
ppm

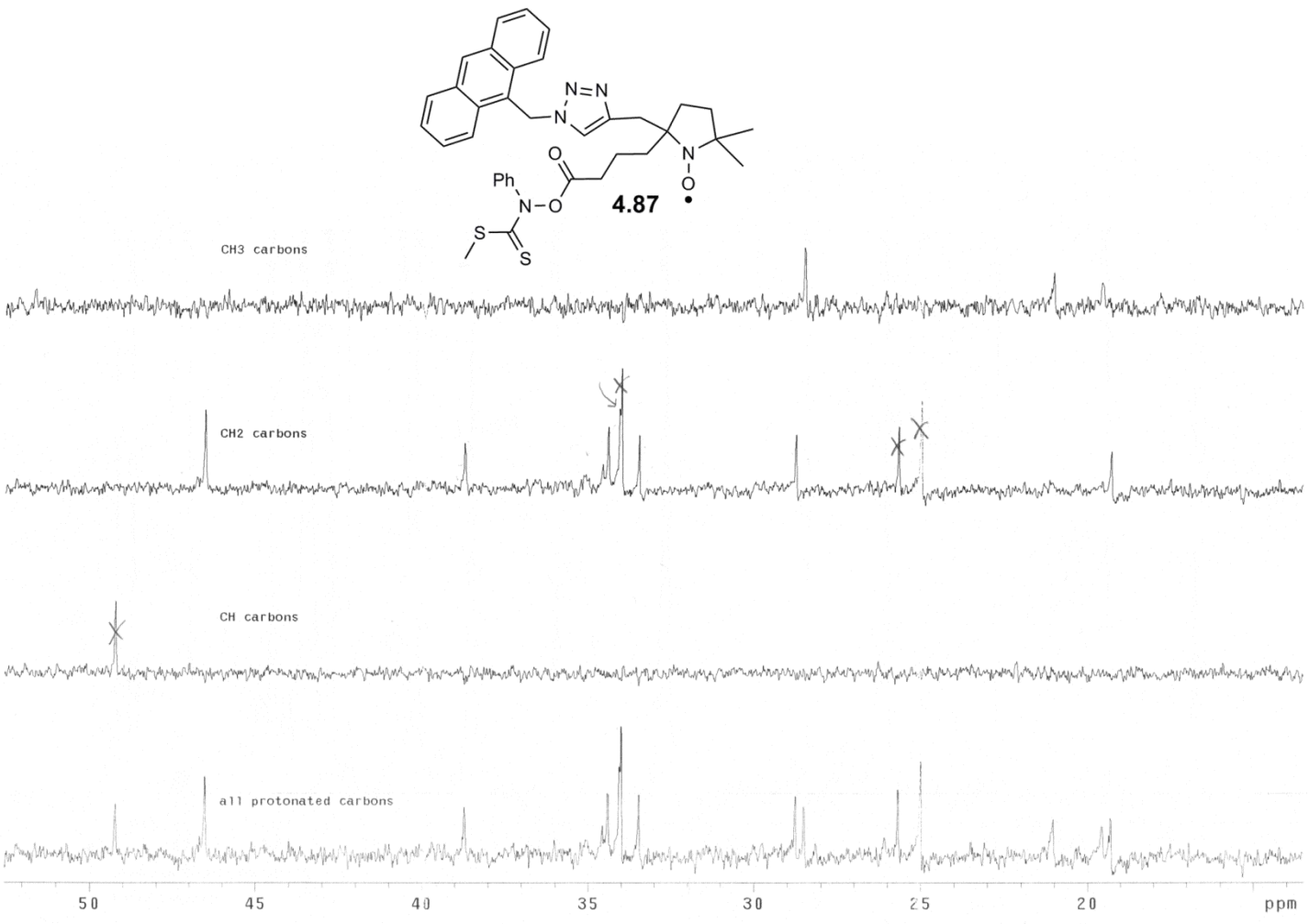
HOOC
N
O
4.82
8
7
6
5
4
3
2
1
ppm

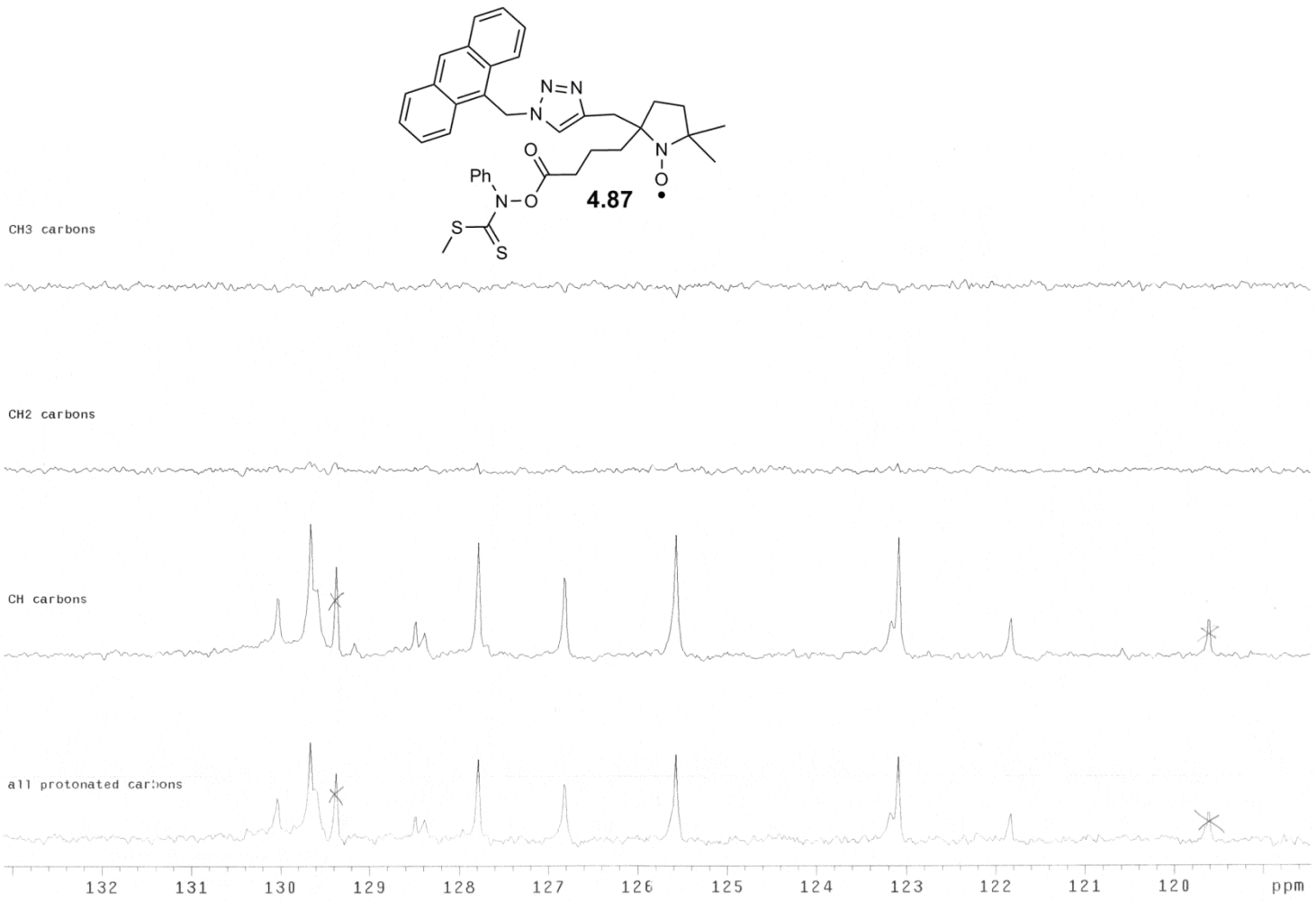

HOOC
N
O
4.82
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


HOOC
N
O
4.82
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm

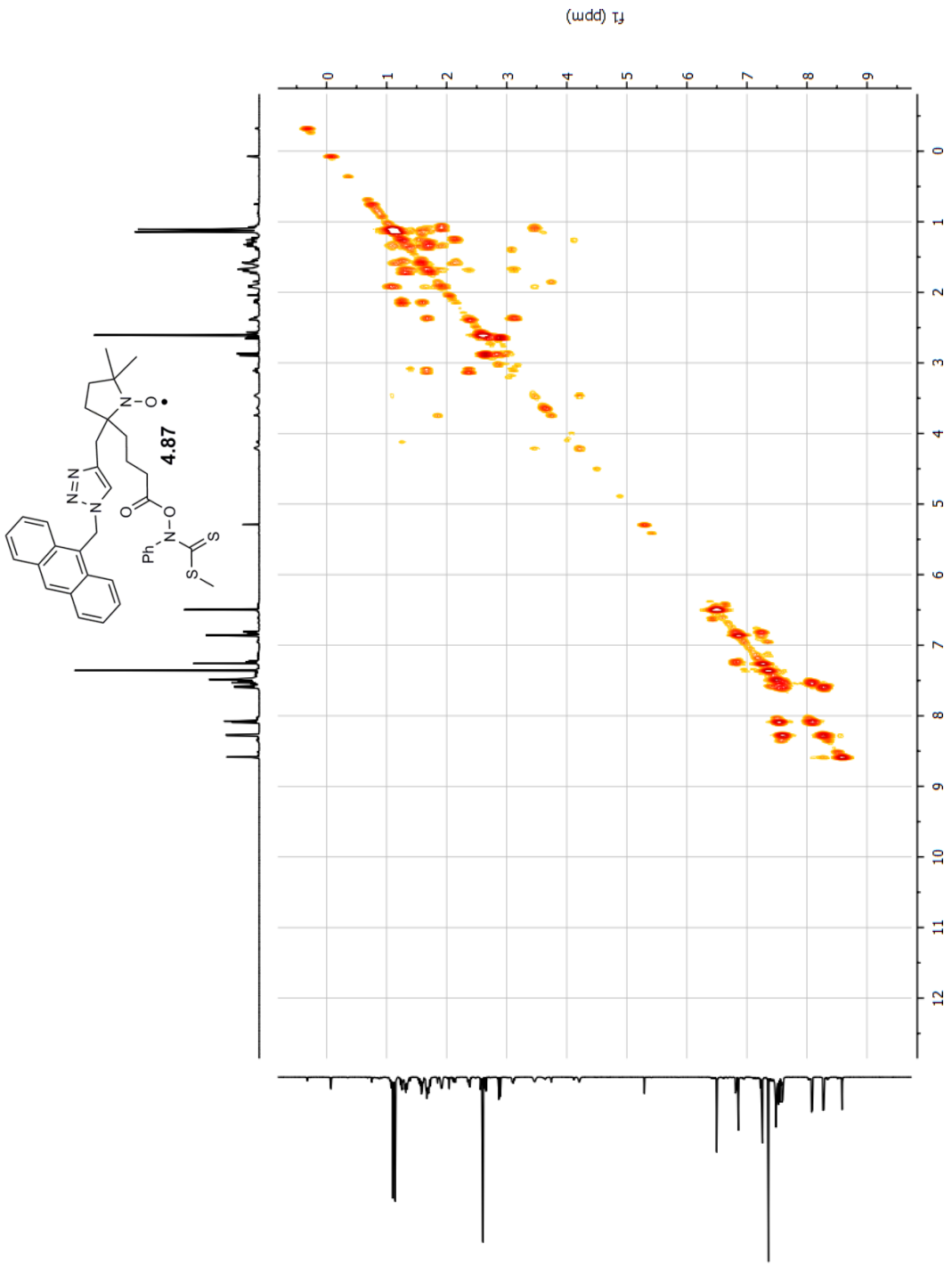

4.87


4.87

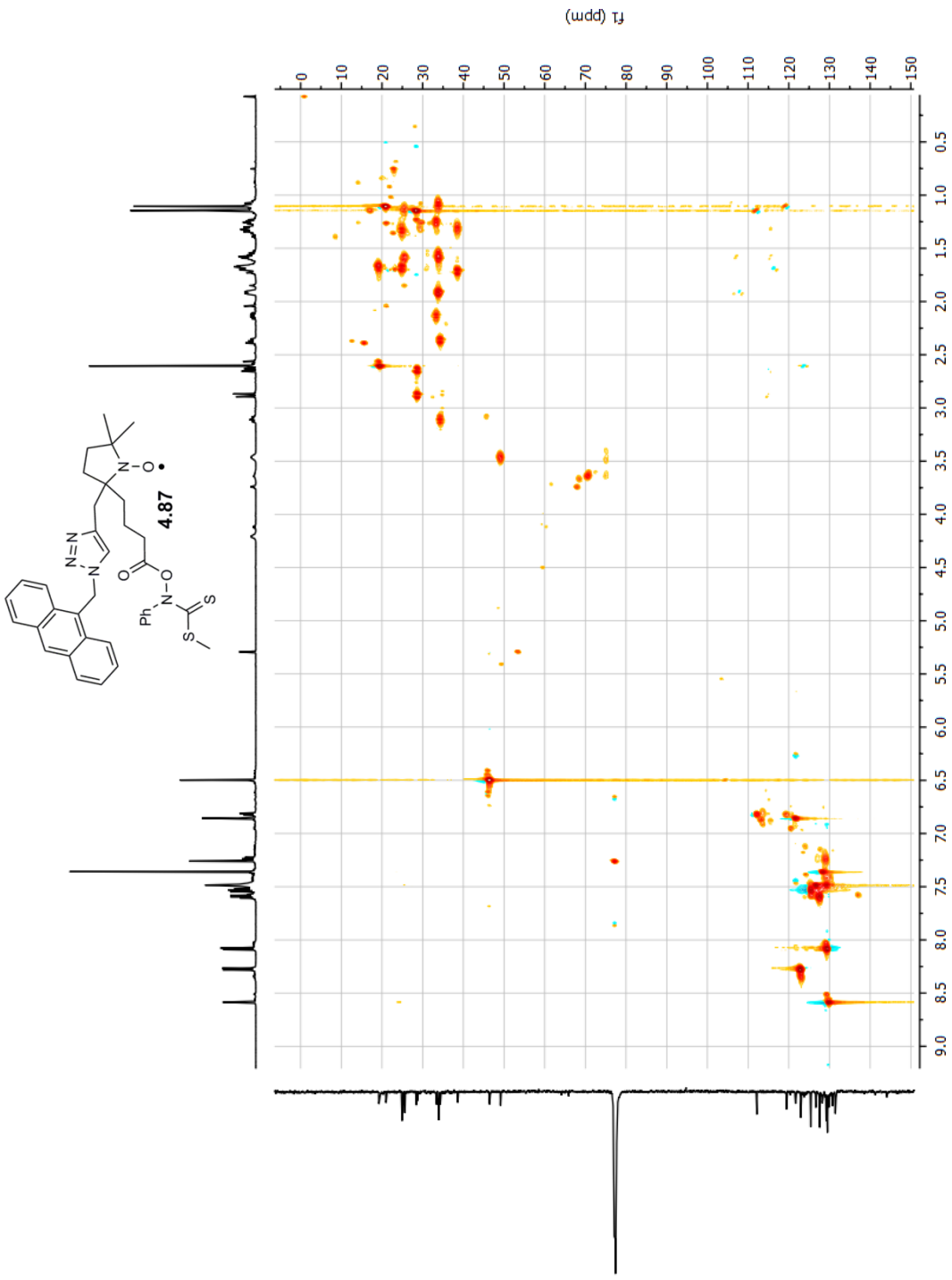

4.87
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
50
45
40
35
30
25
20
ppm


4.87
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
132
131
130
129
128
127
126
125
124
123
122
121
120
ppm

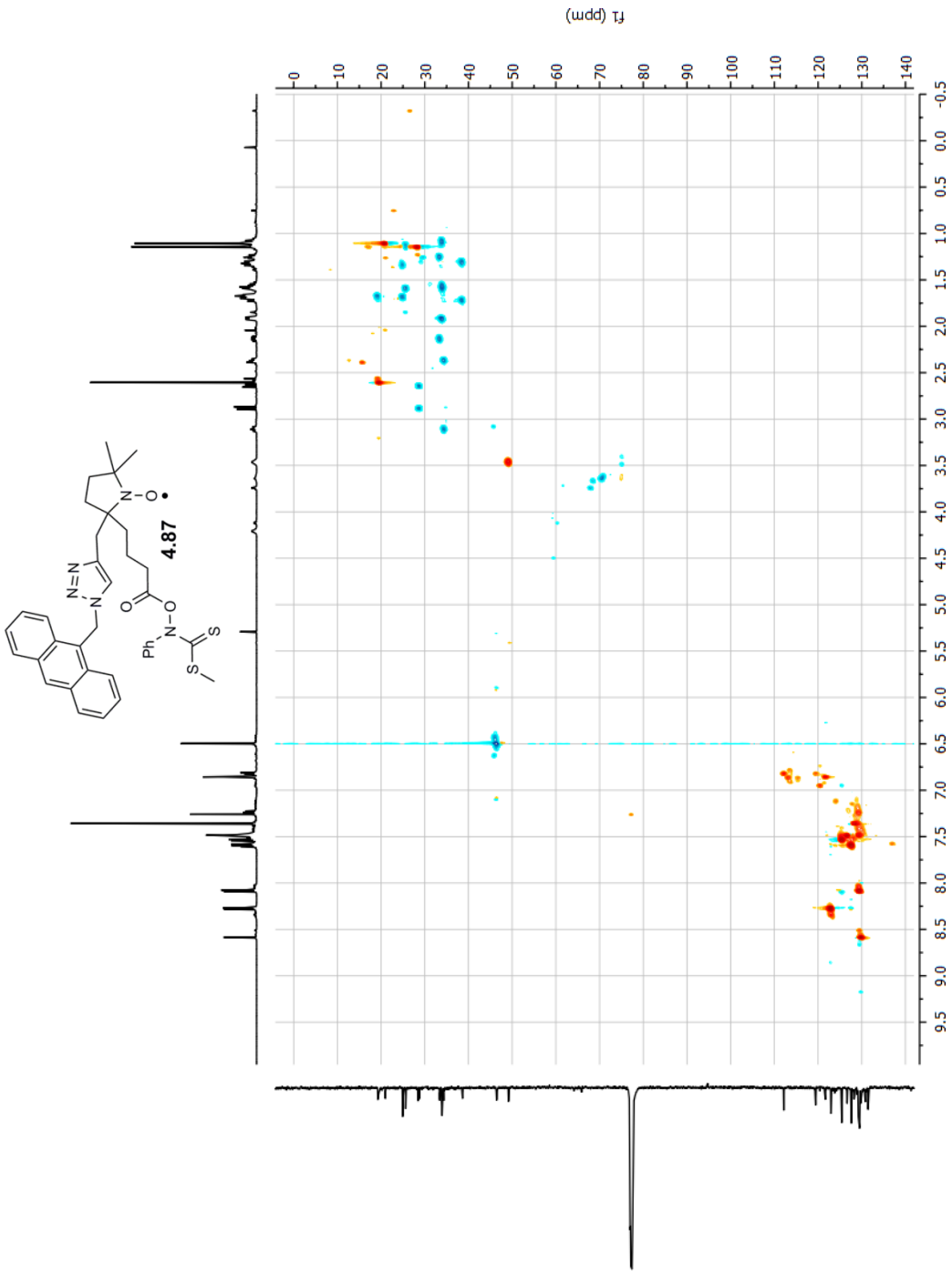
COSY



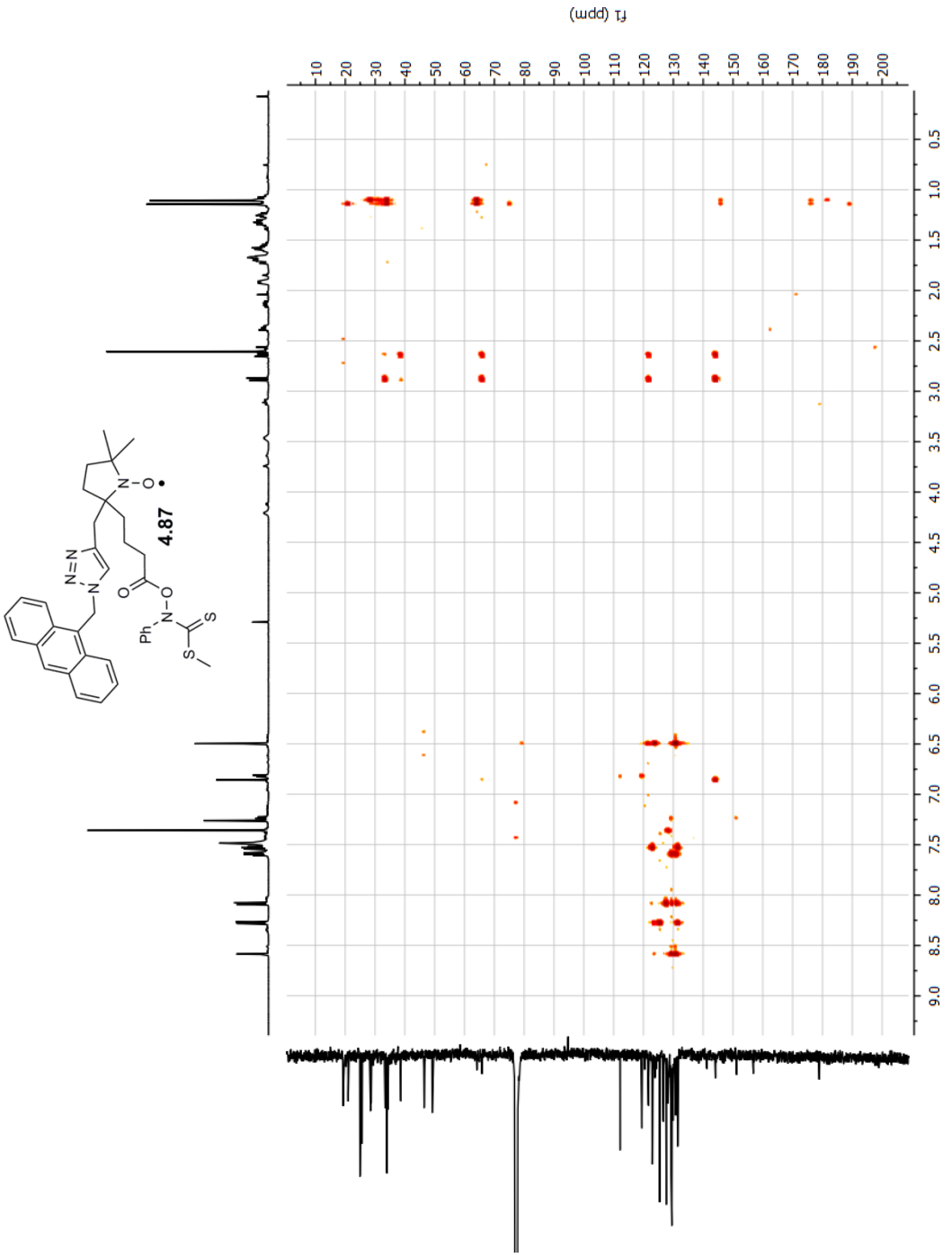
HMQC

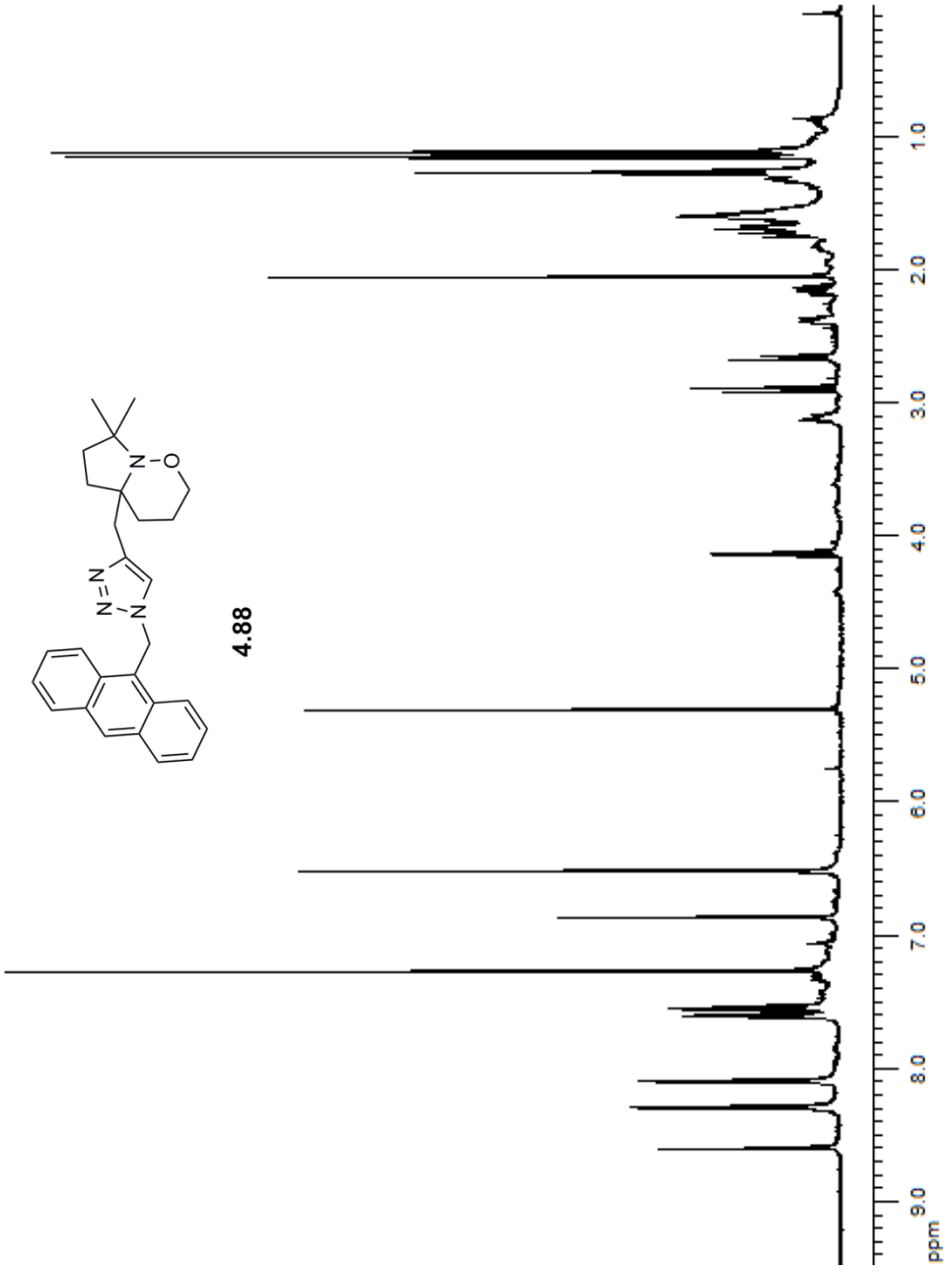


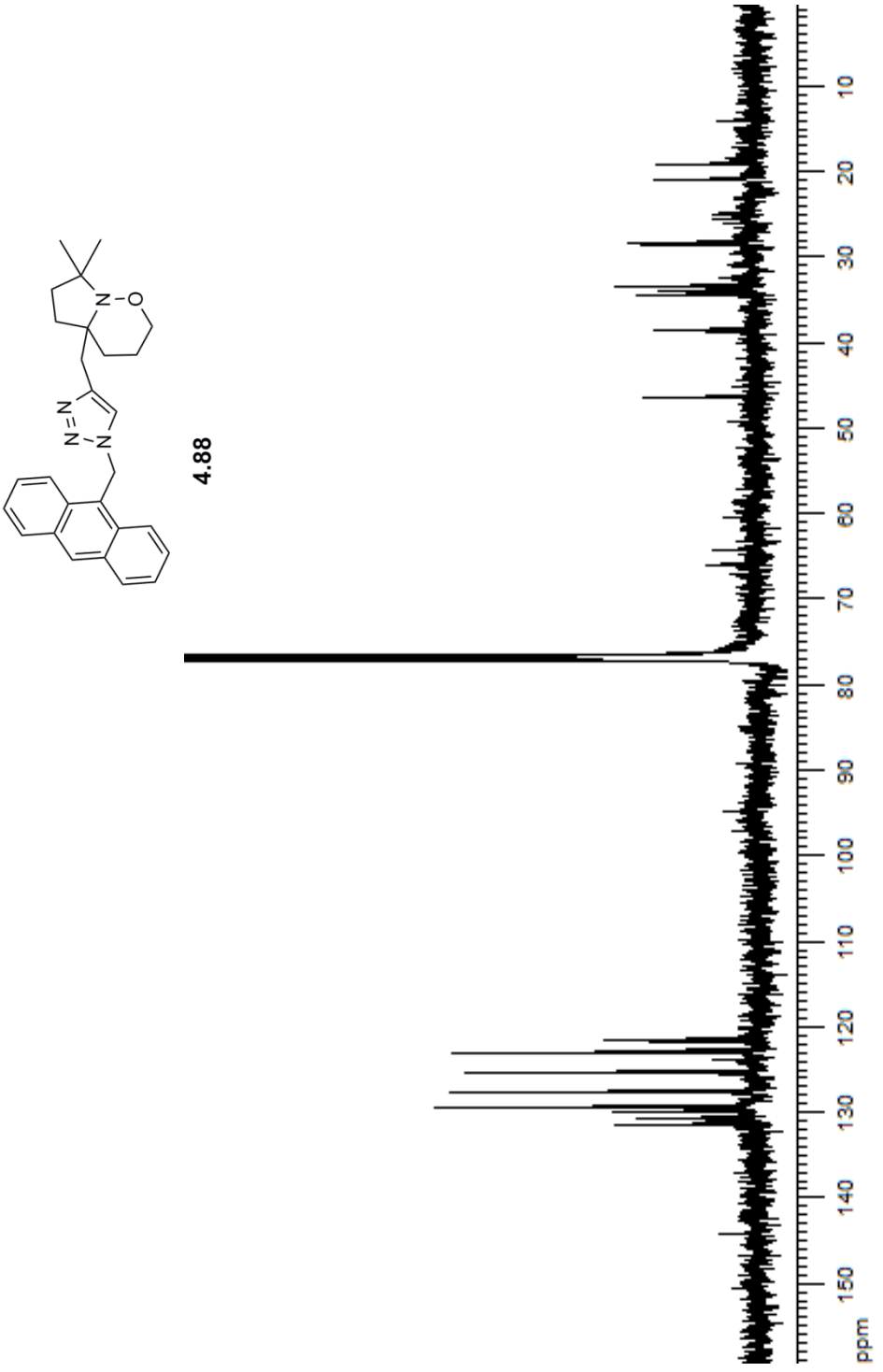
HSQC

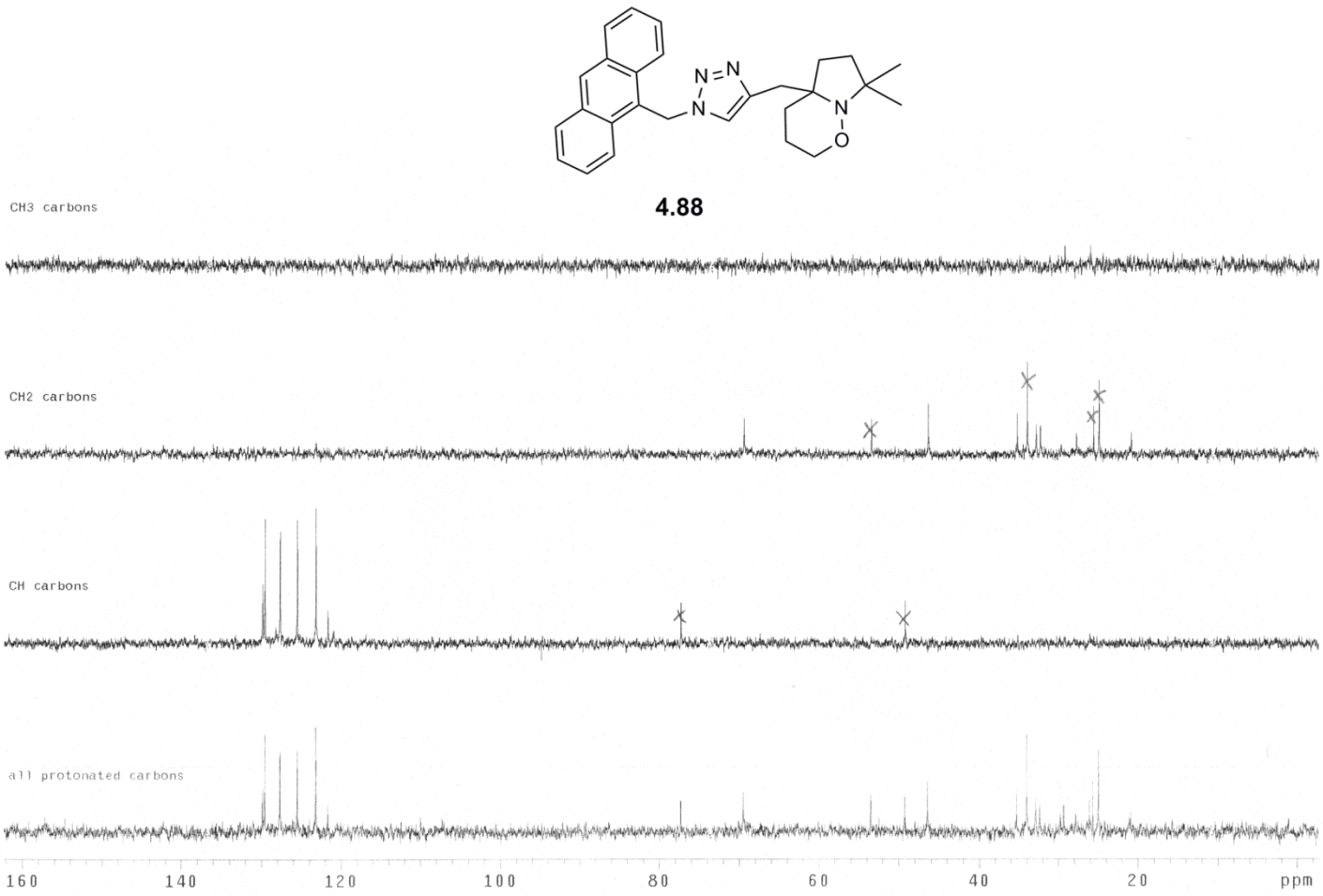


HMBC

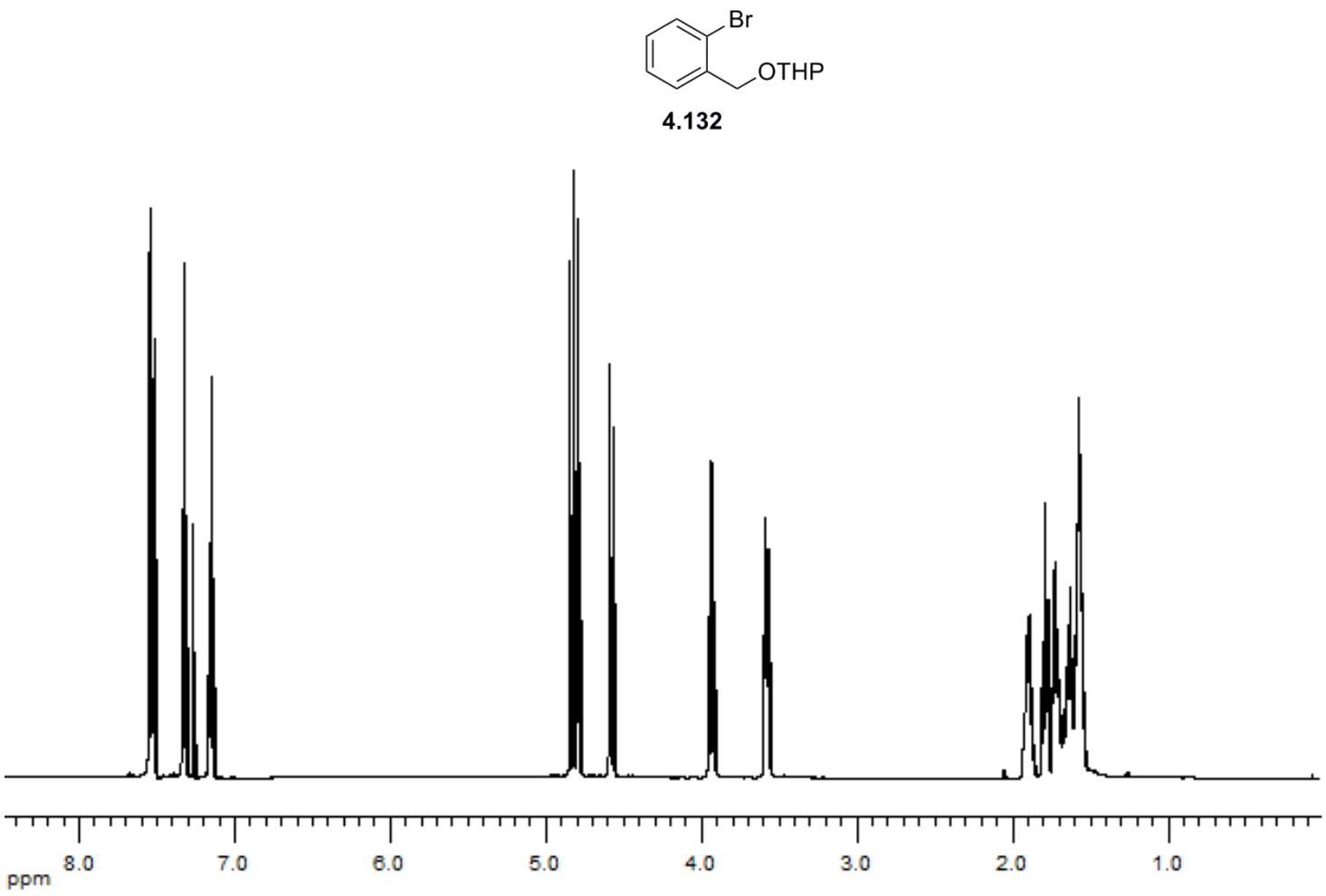


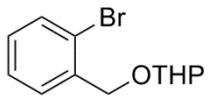

4.88
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


4.88
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm

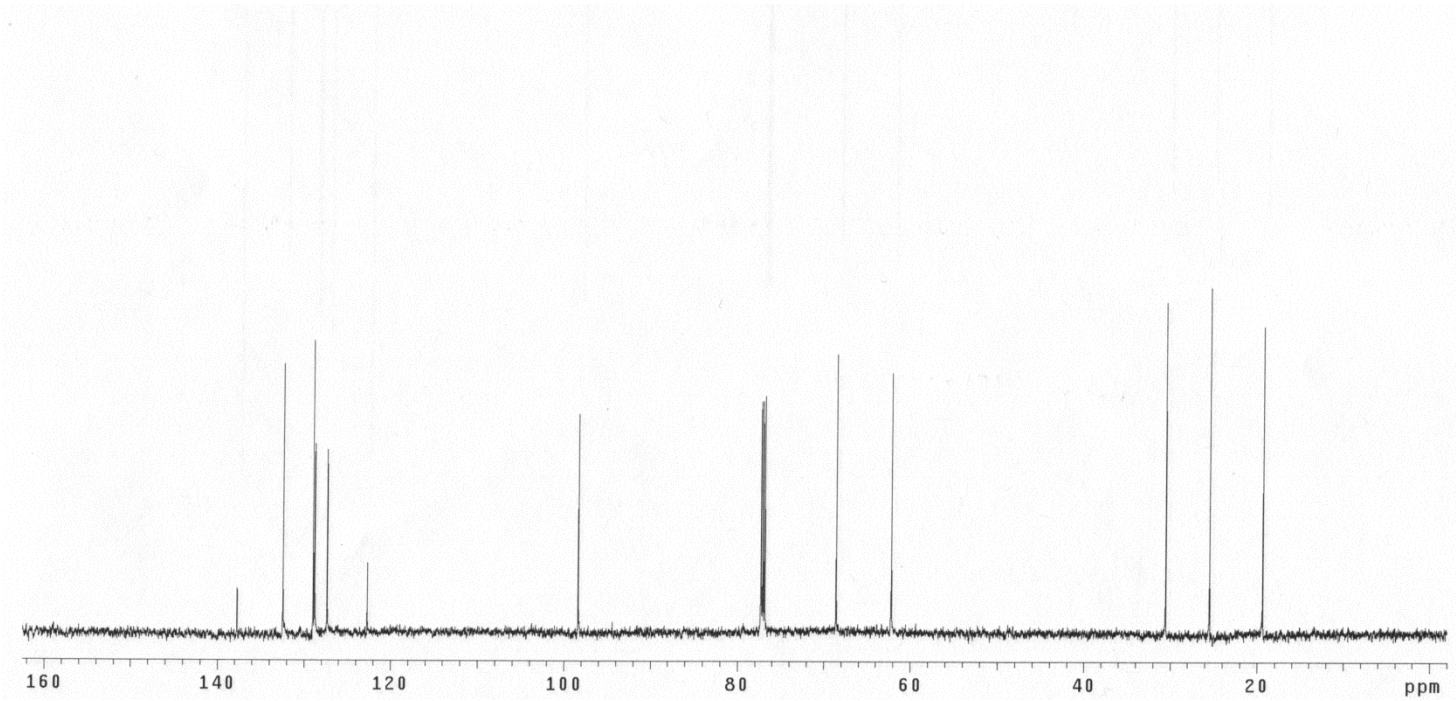

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm

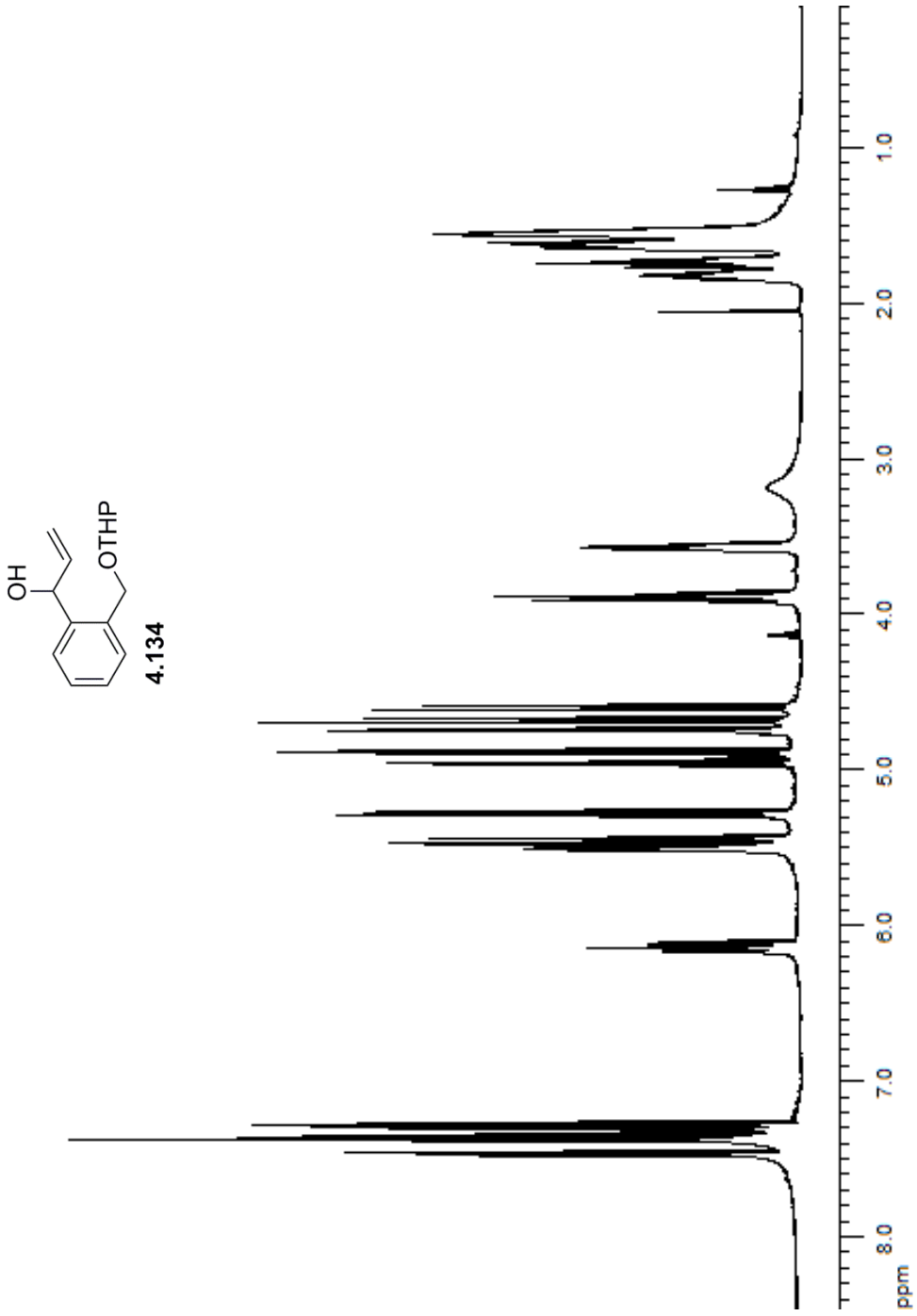
4.88

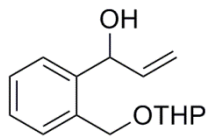

Br
OTHP
4.132
ppm
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0



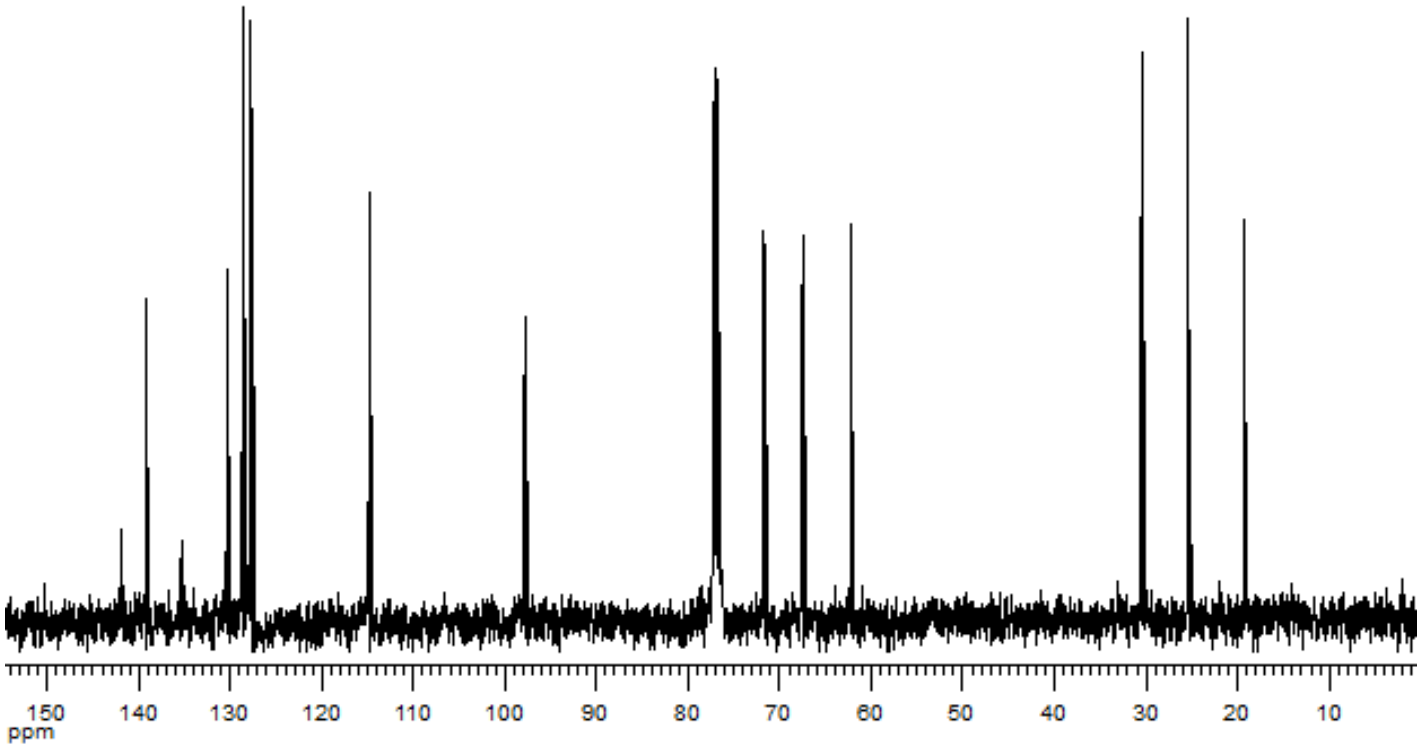
4.132

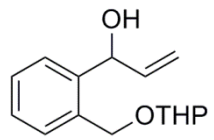



OH
OTHP
4.134
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

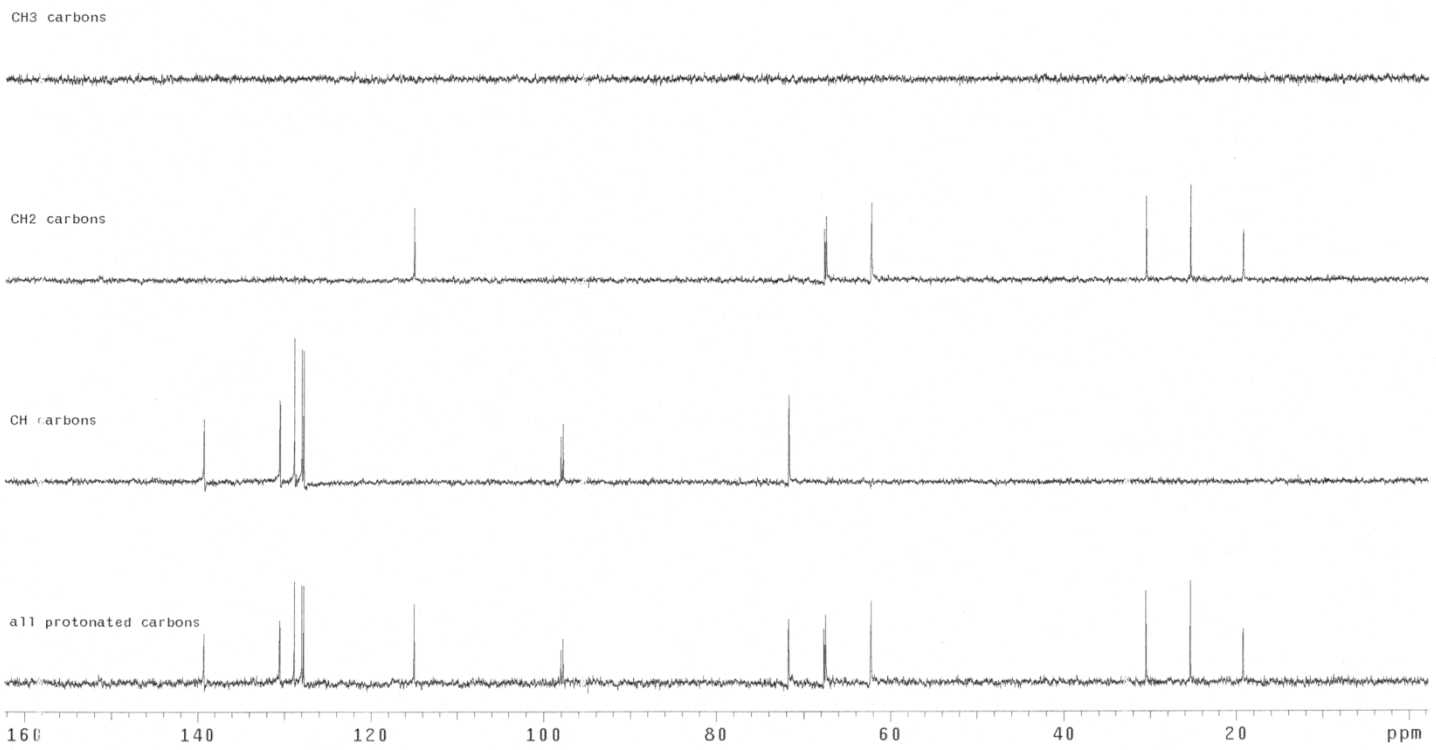


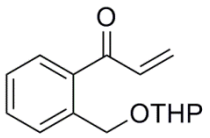
4.134



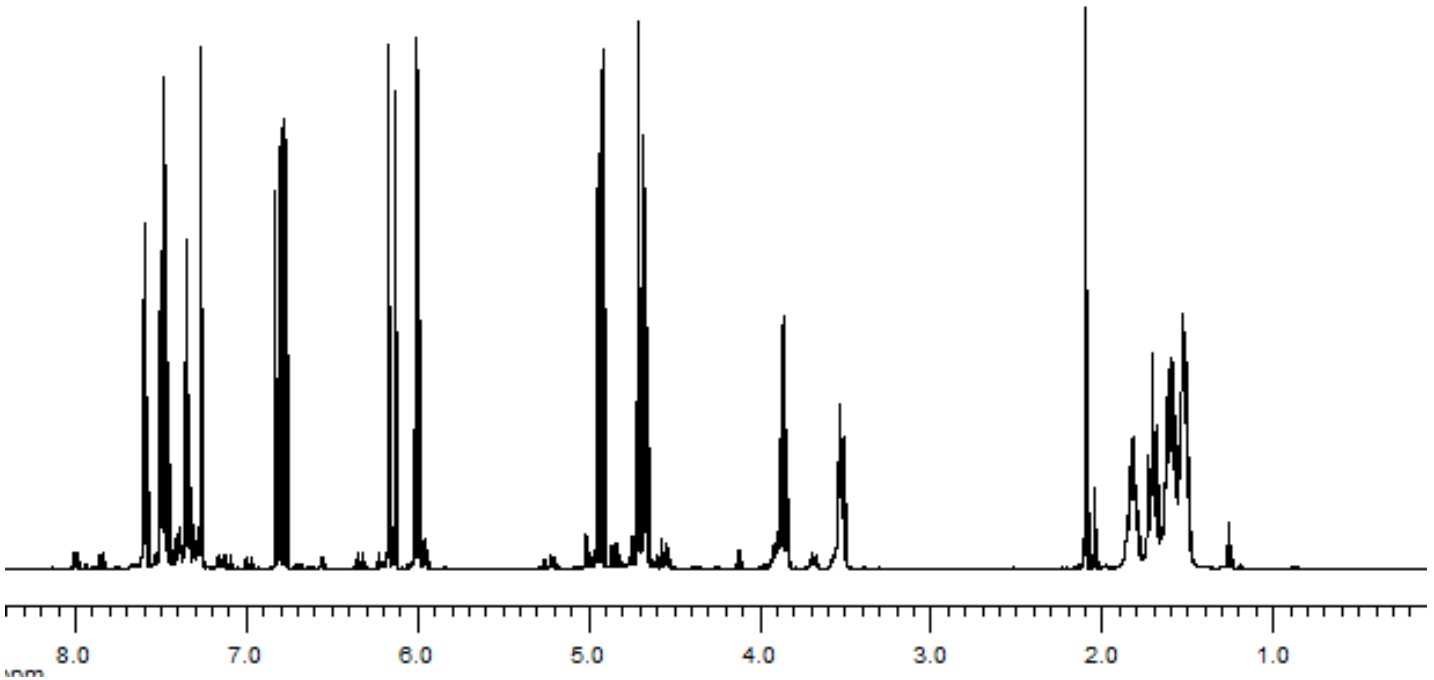

OH
OTHP

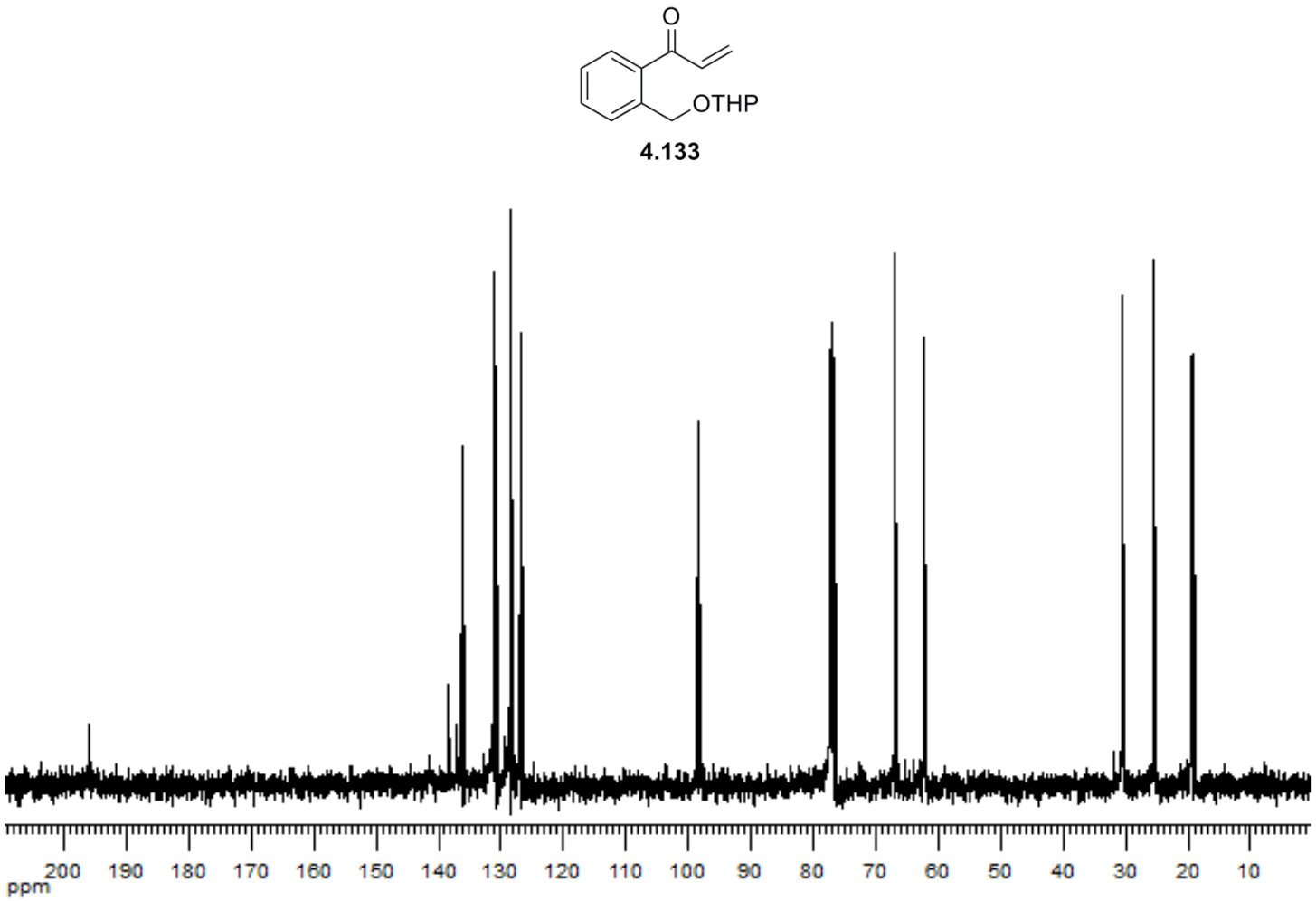
4.134

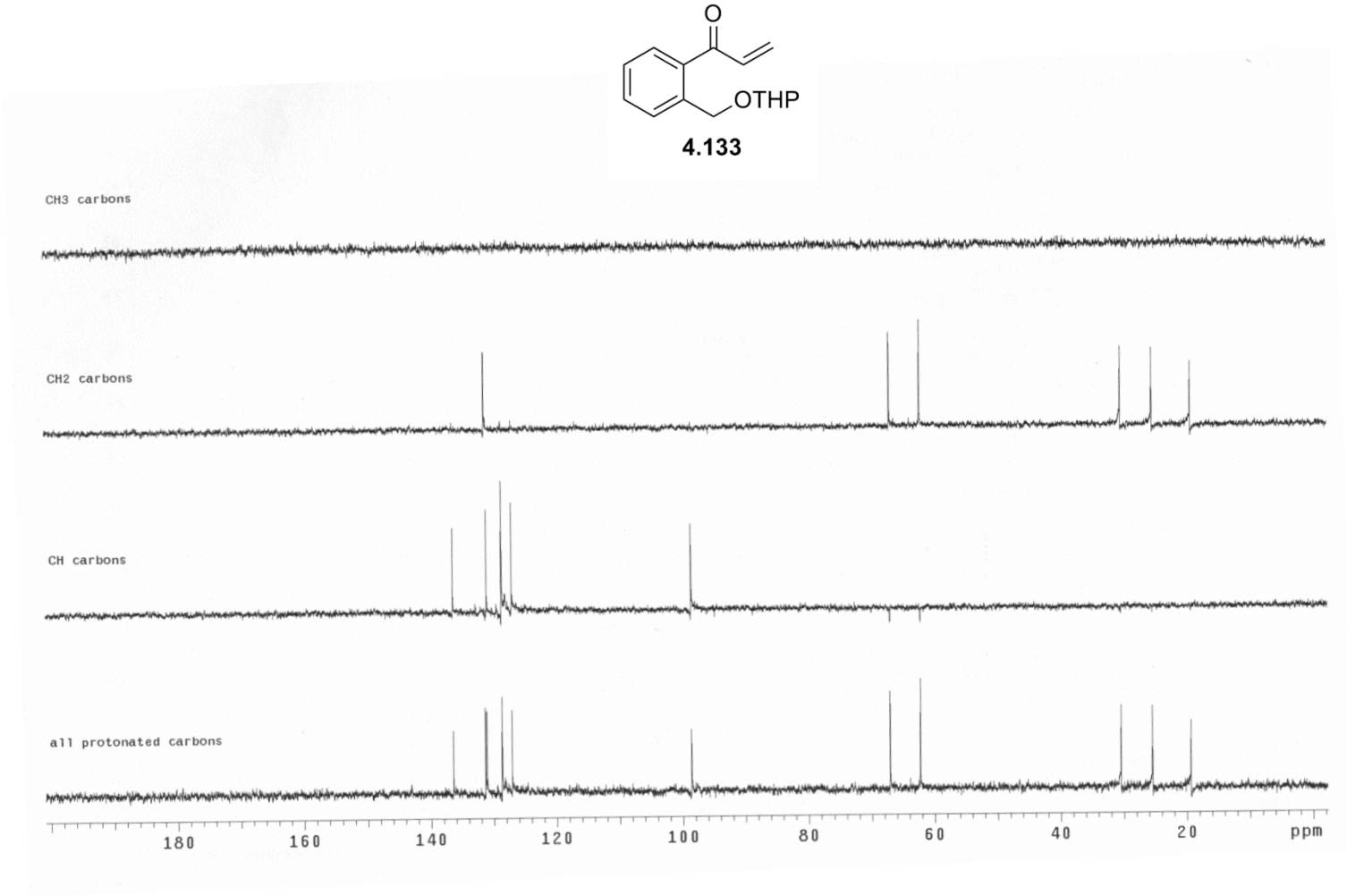

CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm

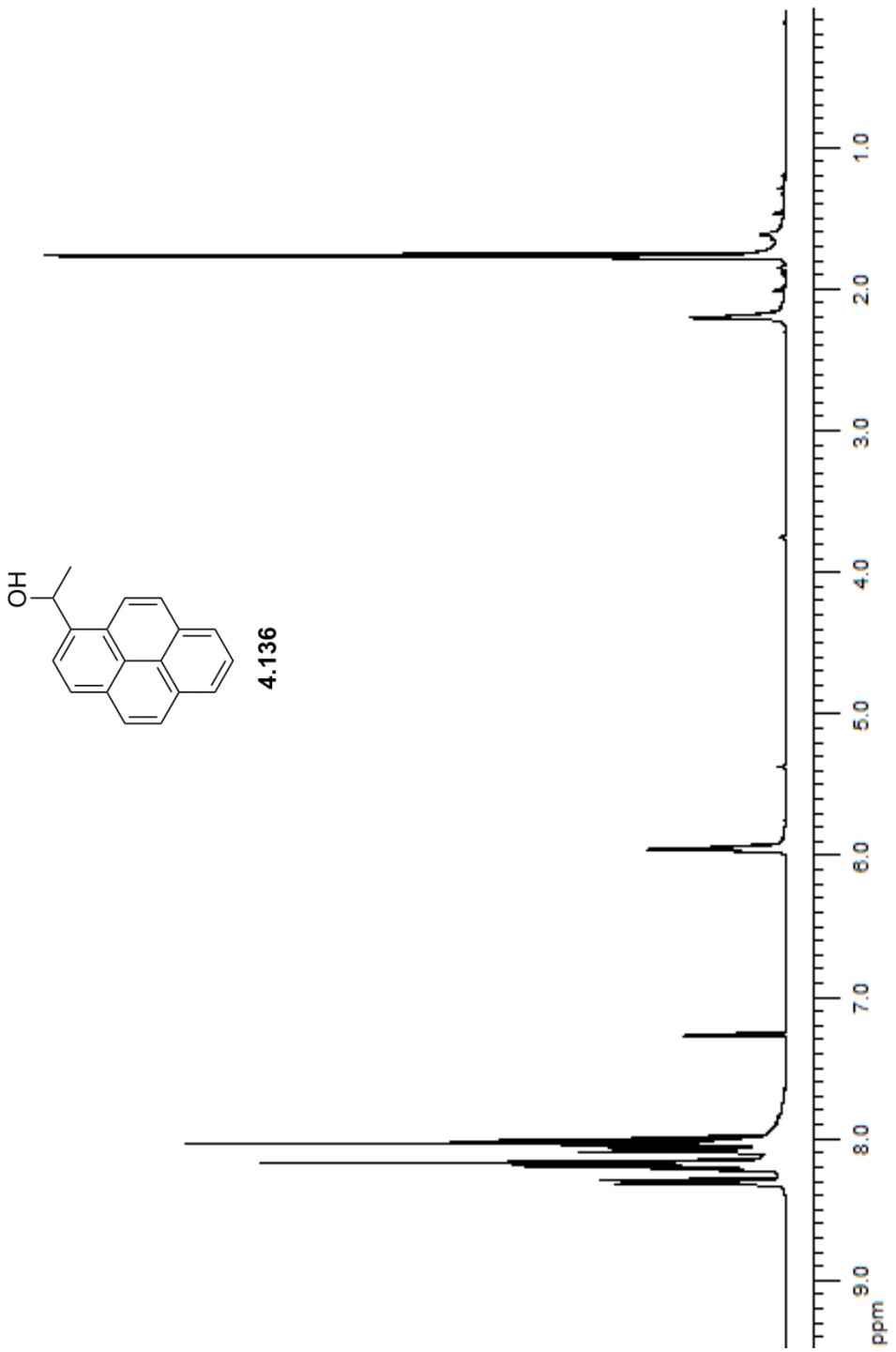


4.133




O
OTHP
4.133
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
OTHP
4.133
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm


OH
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7.0
6.0
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4.0
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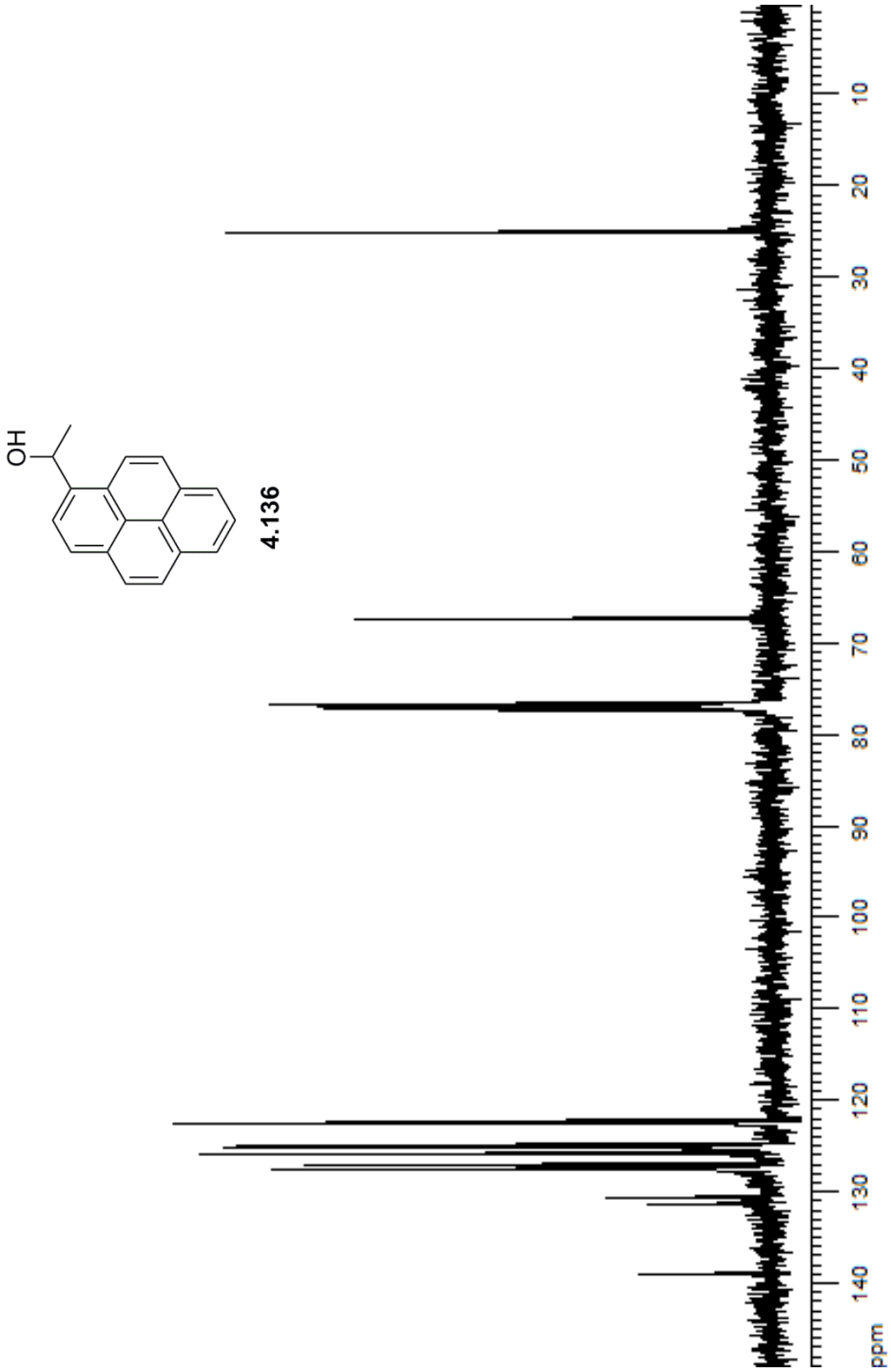
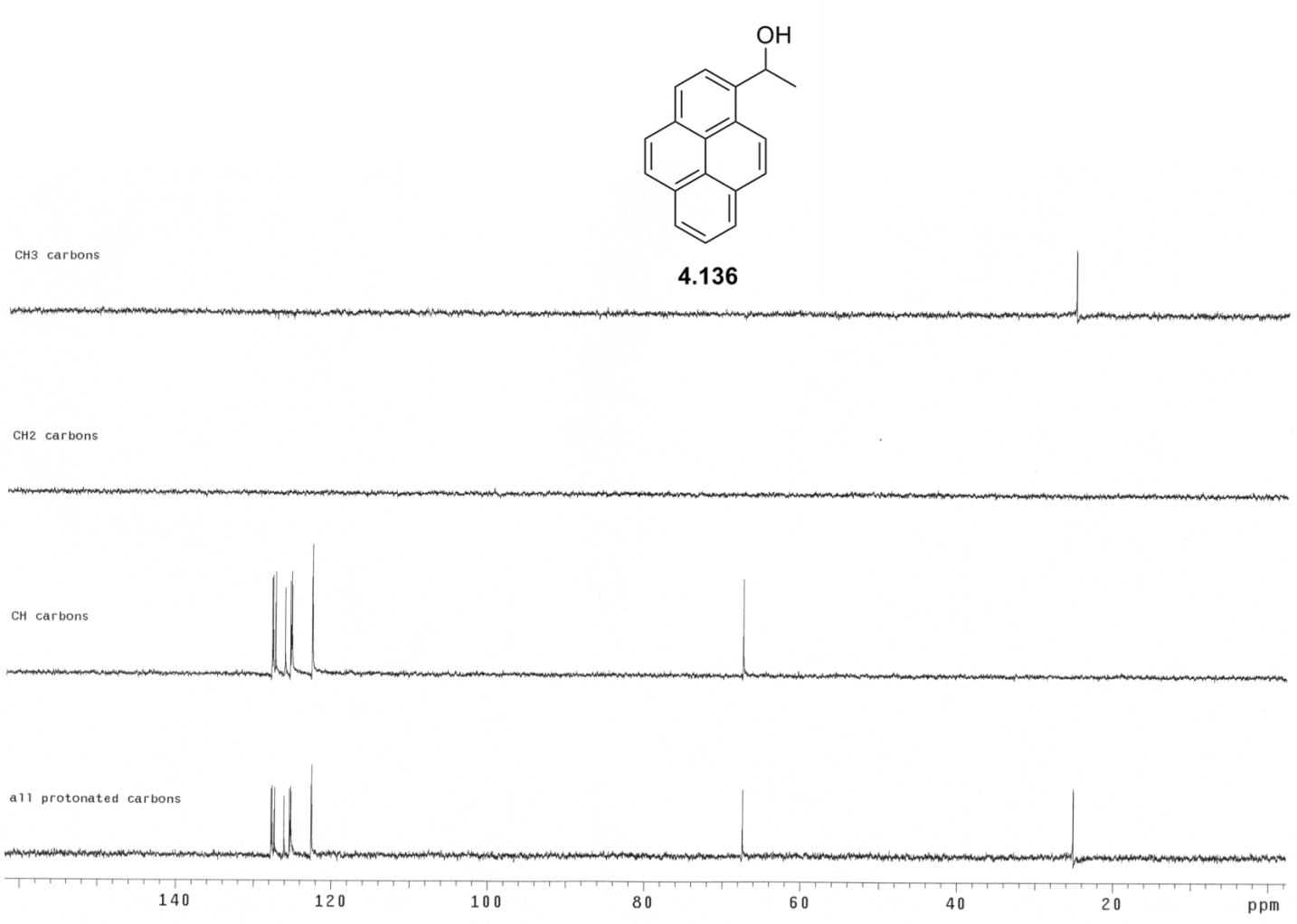
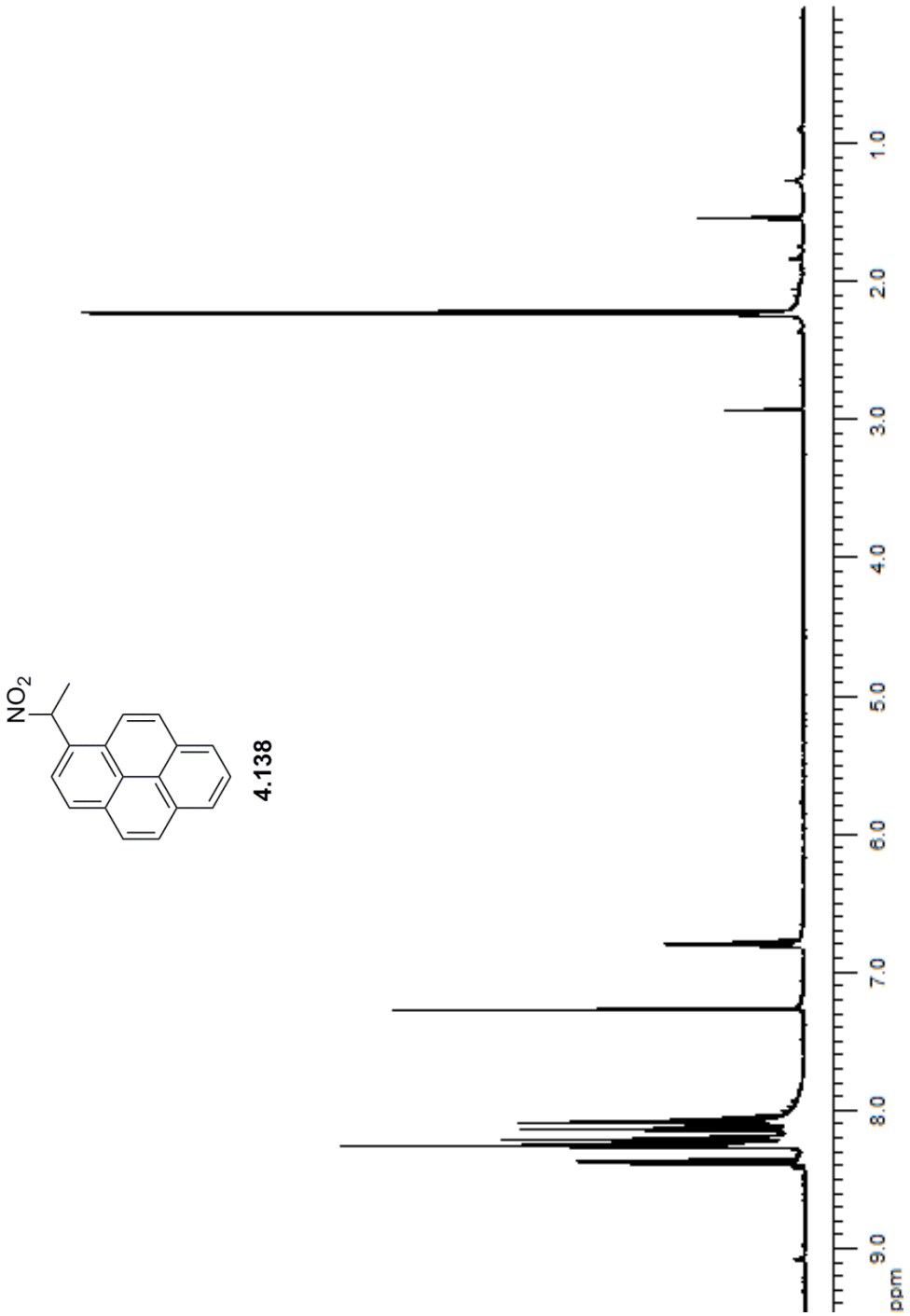
ppm


OH
4.136
10
20
30
40
50
60
70
80
90
100
110
120
130
140
ppm


OH
4.136
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
140
120
100
80
60
40
20
ppm


NO2
4.138
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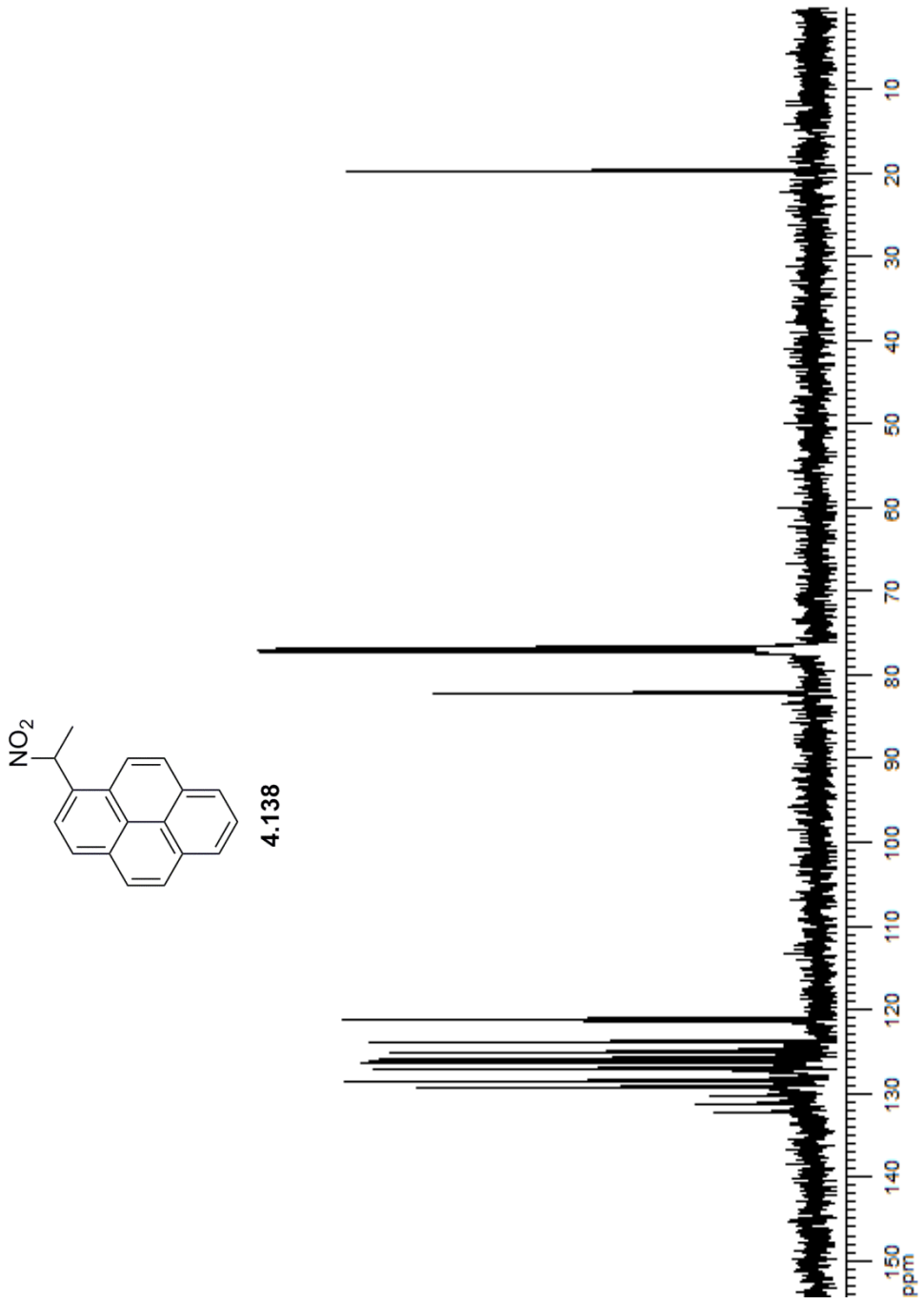
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm


NO2
4.138
10
20
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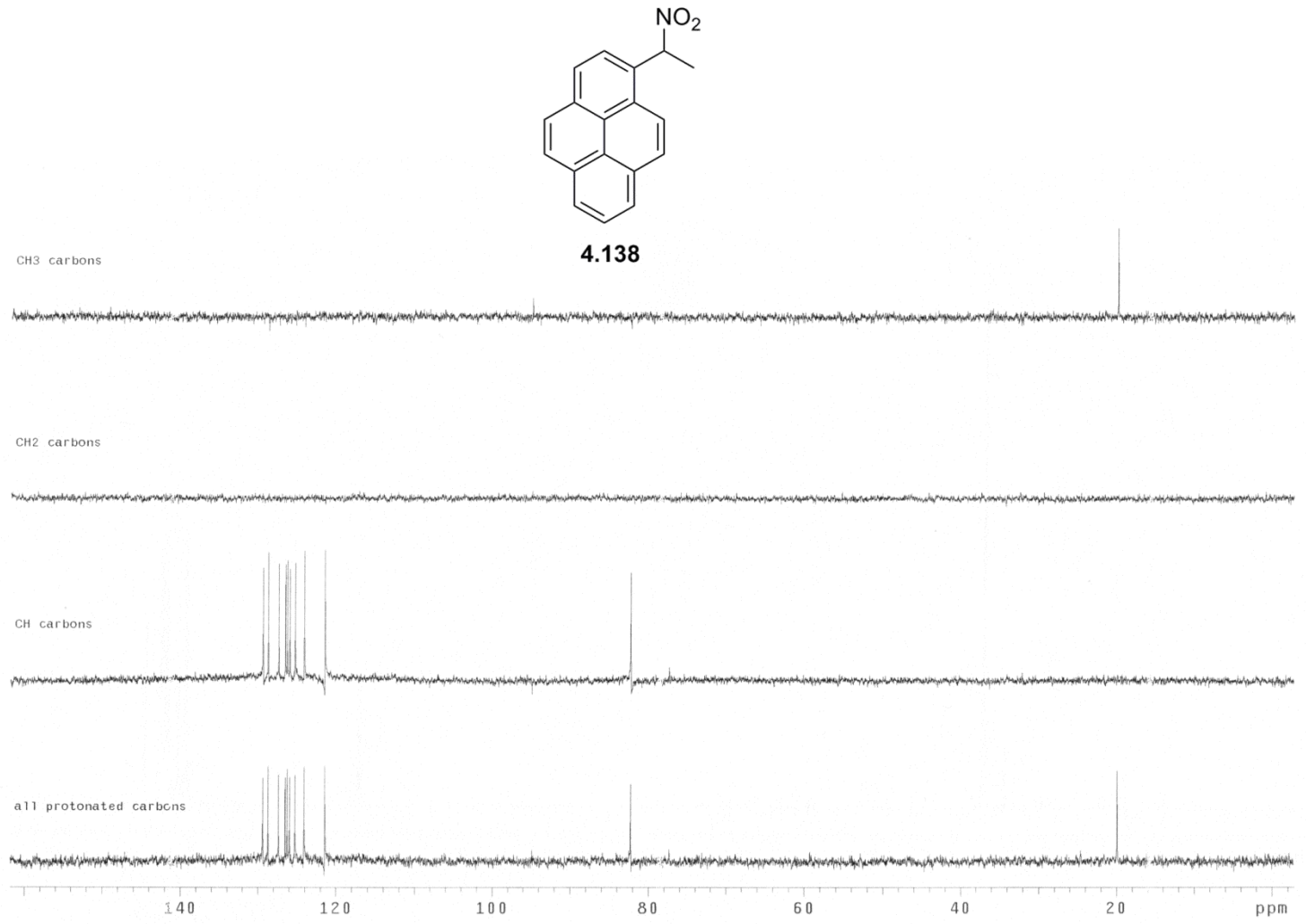
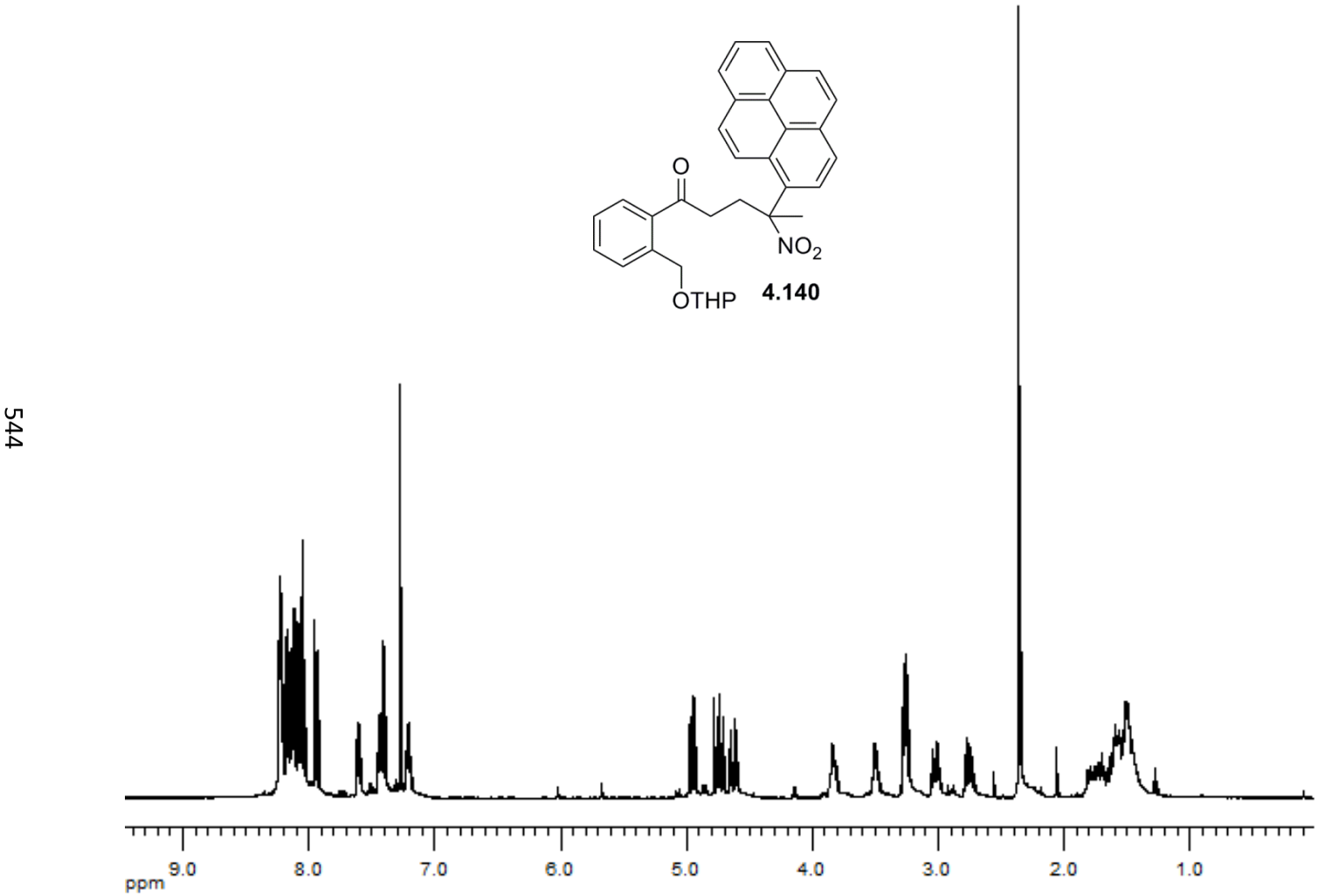
40
50
60
70
80
90
100
110
120
130
140
150
ppm


NO2
4.138
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
140
120
100
80
60
40
20
ppm


O
NO2
OTHP
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ppm
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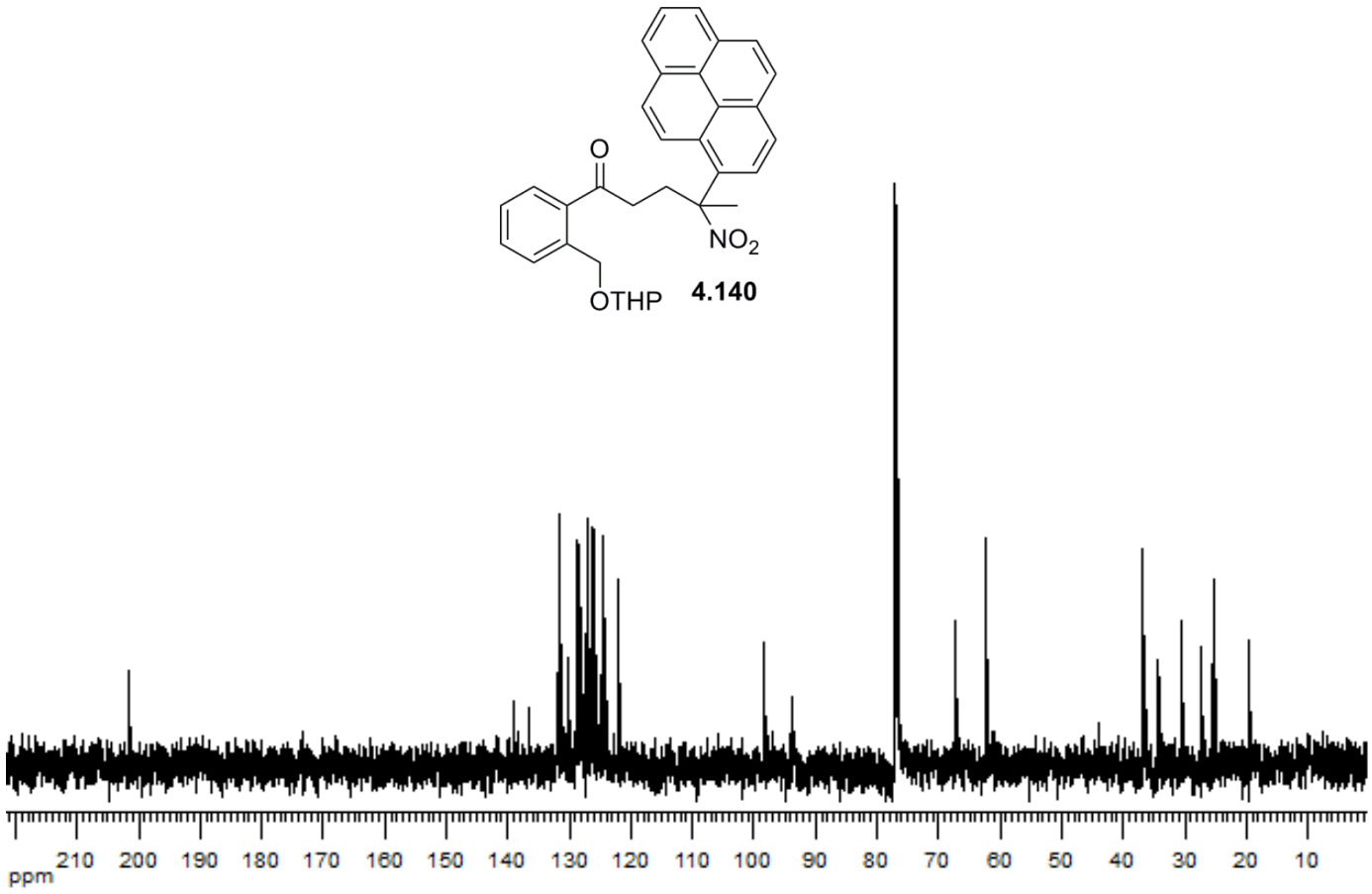
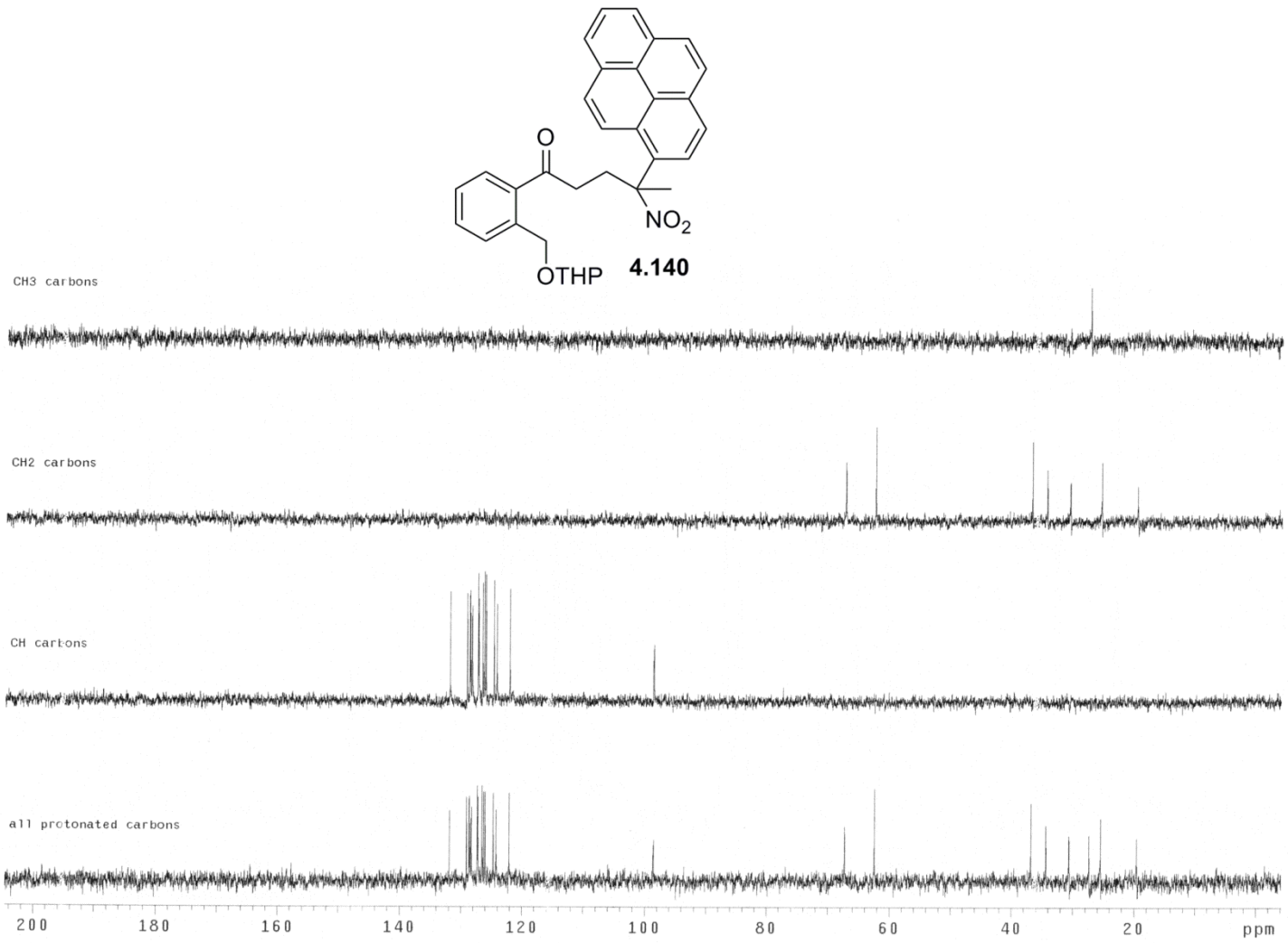
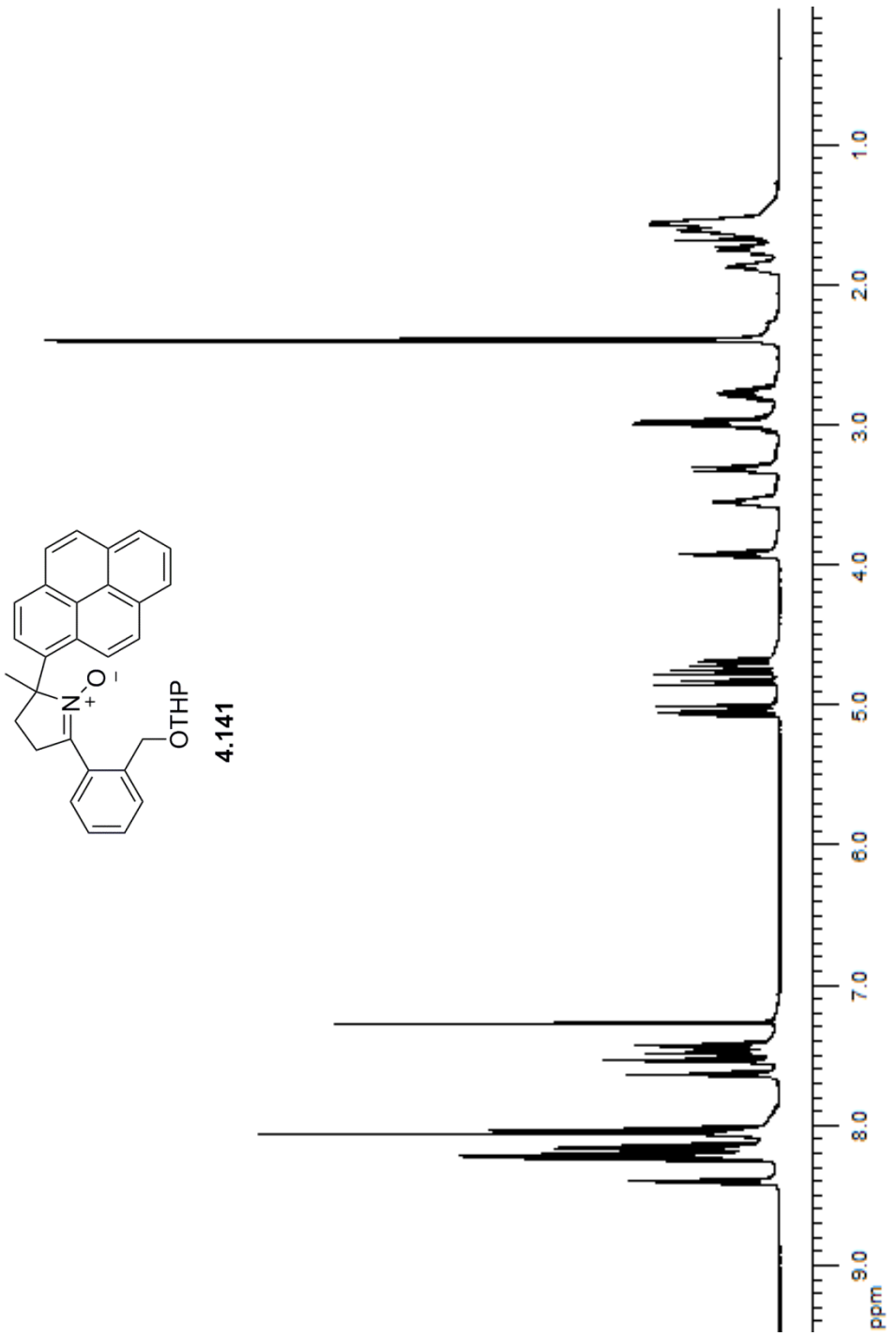
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


O
NO2
OTHP
4.140
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


O
NO2
OTHP
4.140
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
ppm


OTHP
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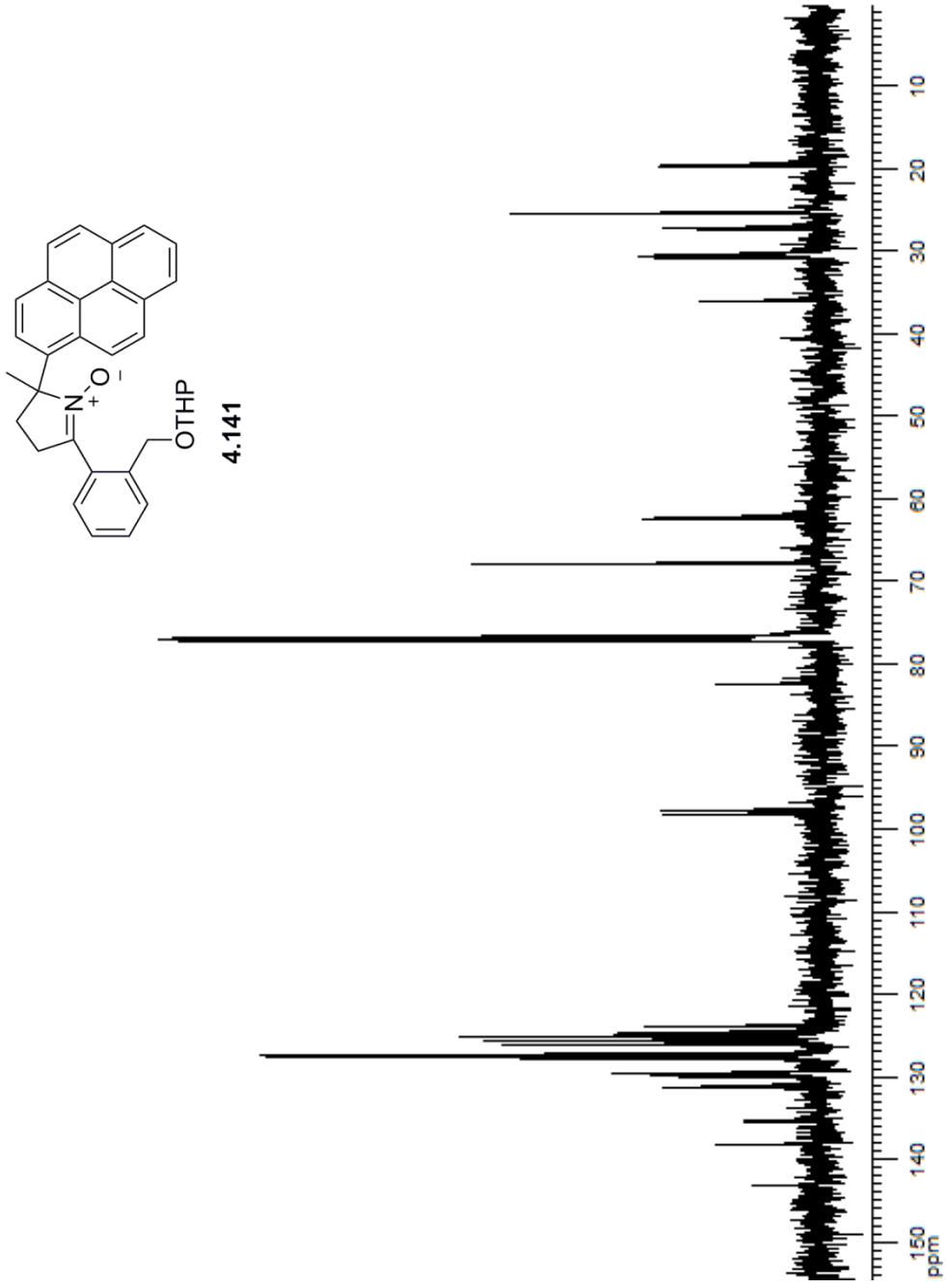
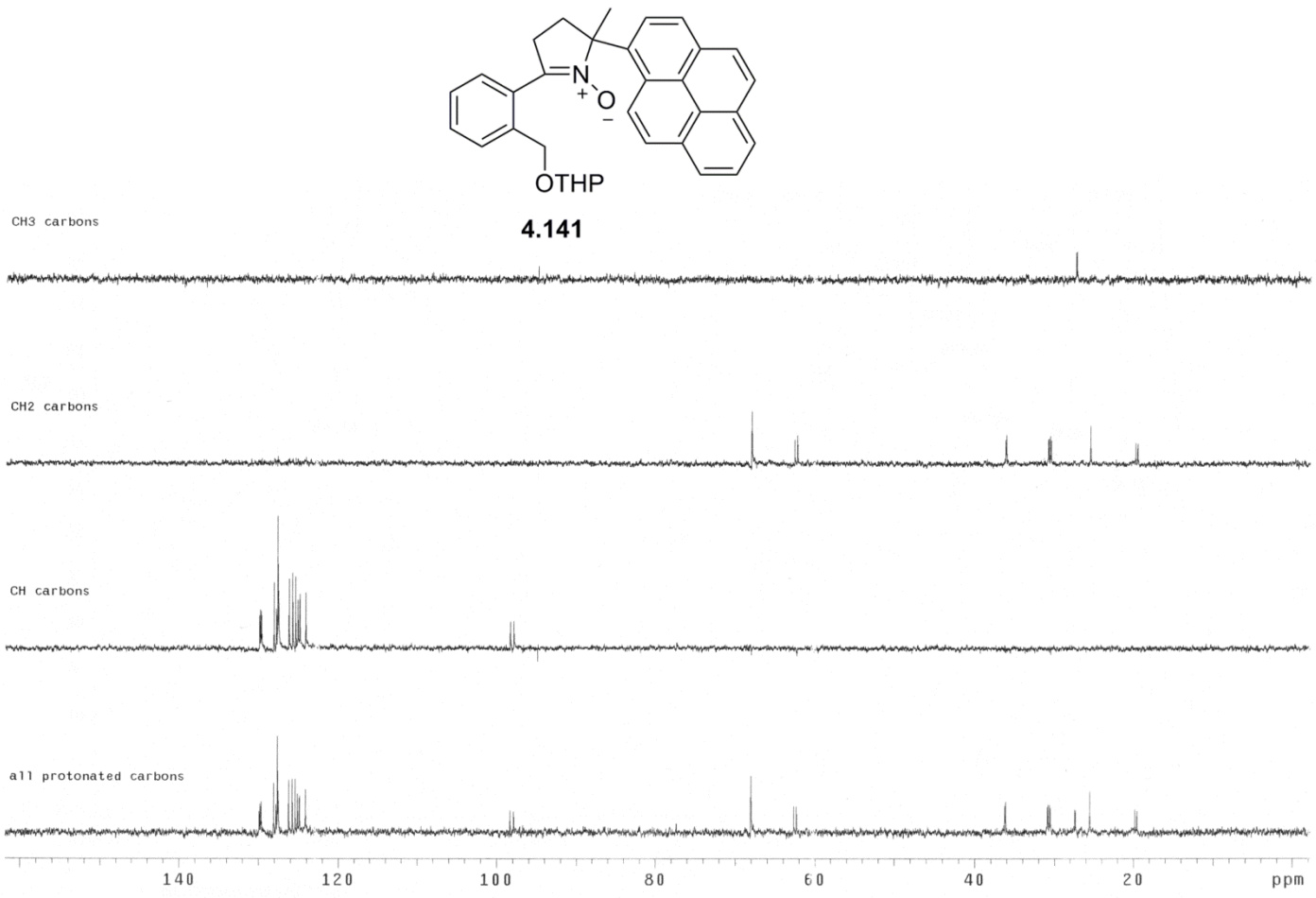
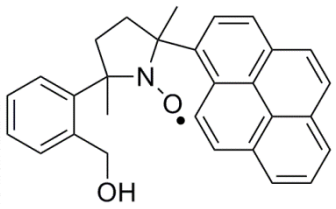
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


OTHP
4.141
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm


OTHP
4.141
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
140
120
100
80
60
40
20
ppm



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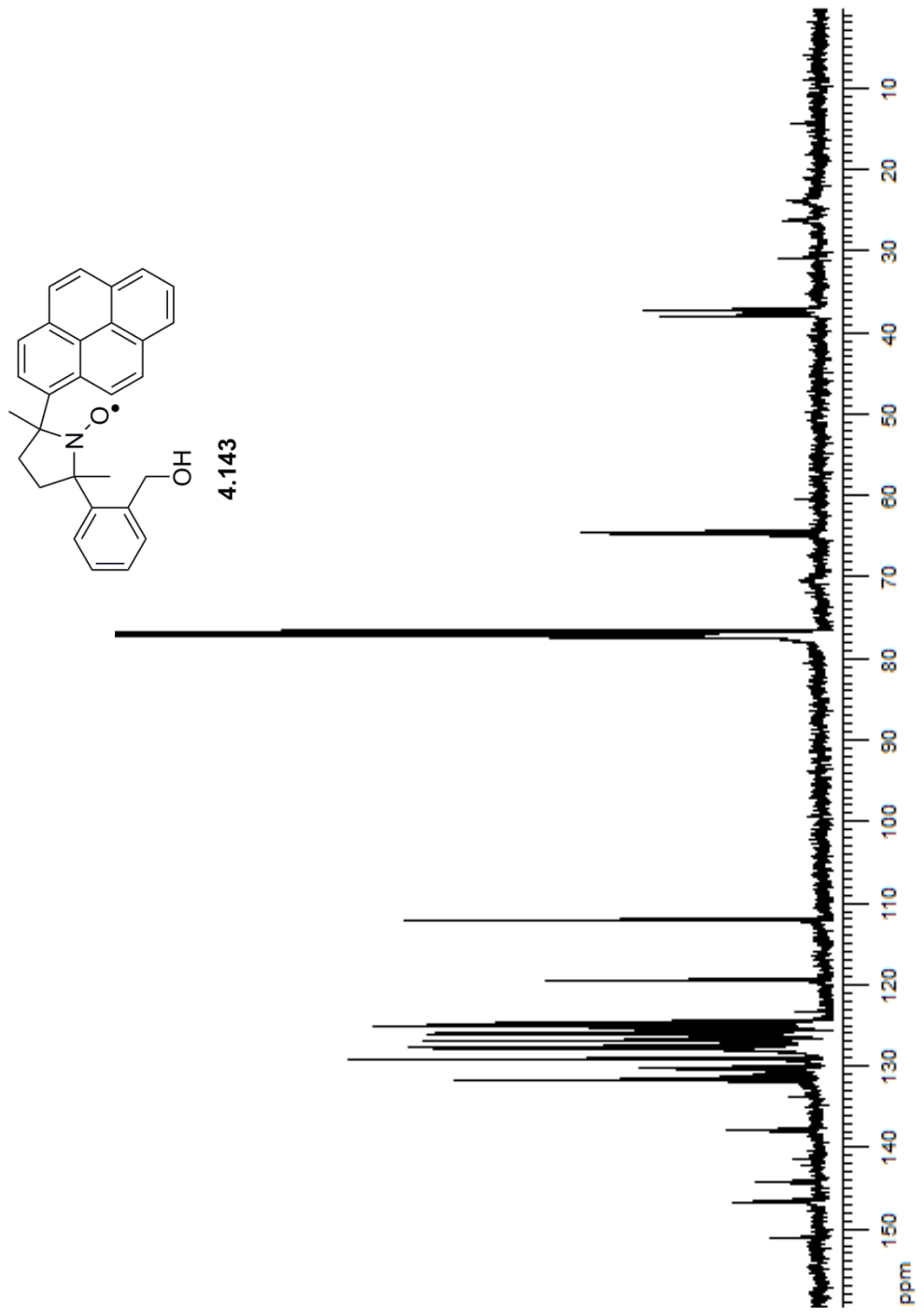
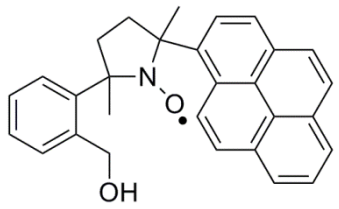
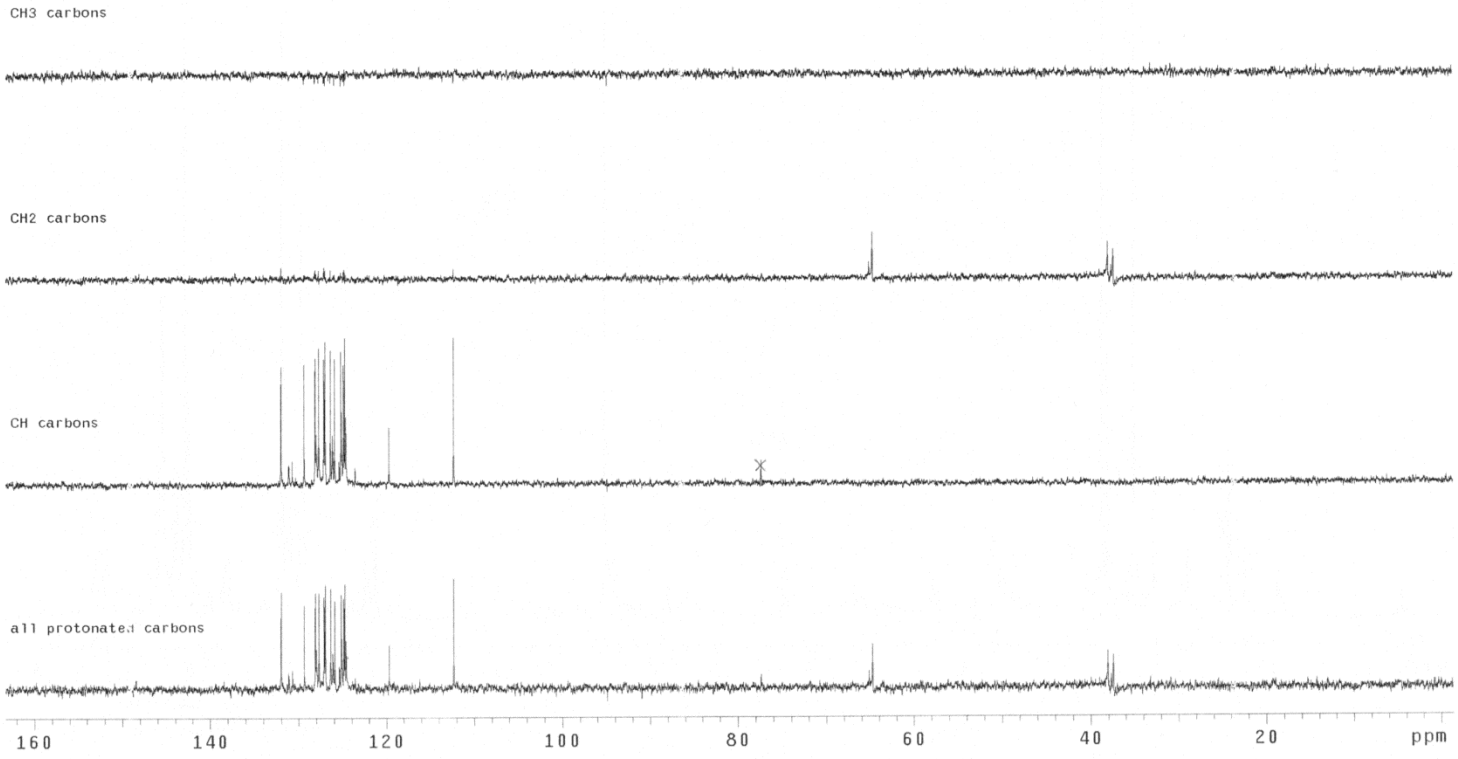
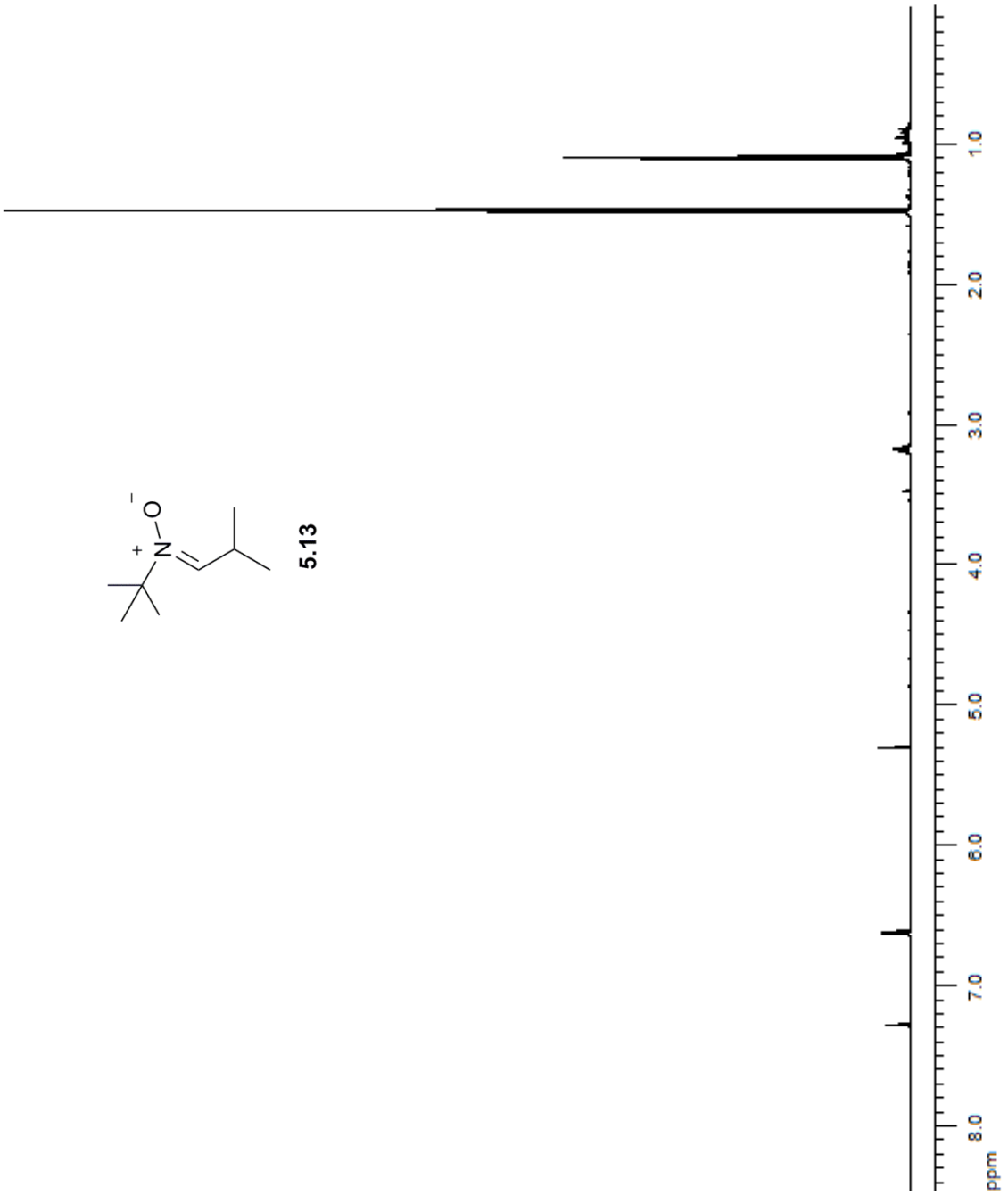
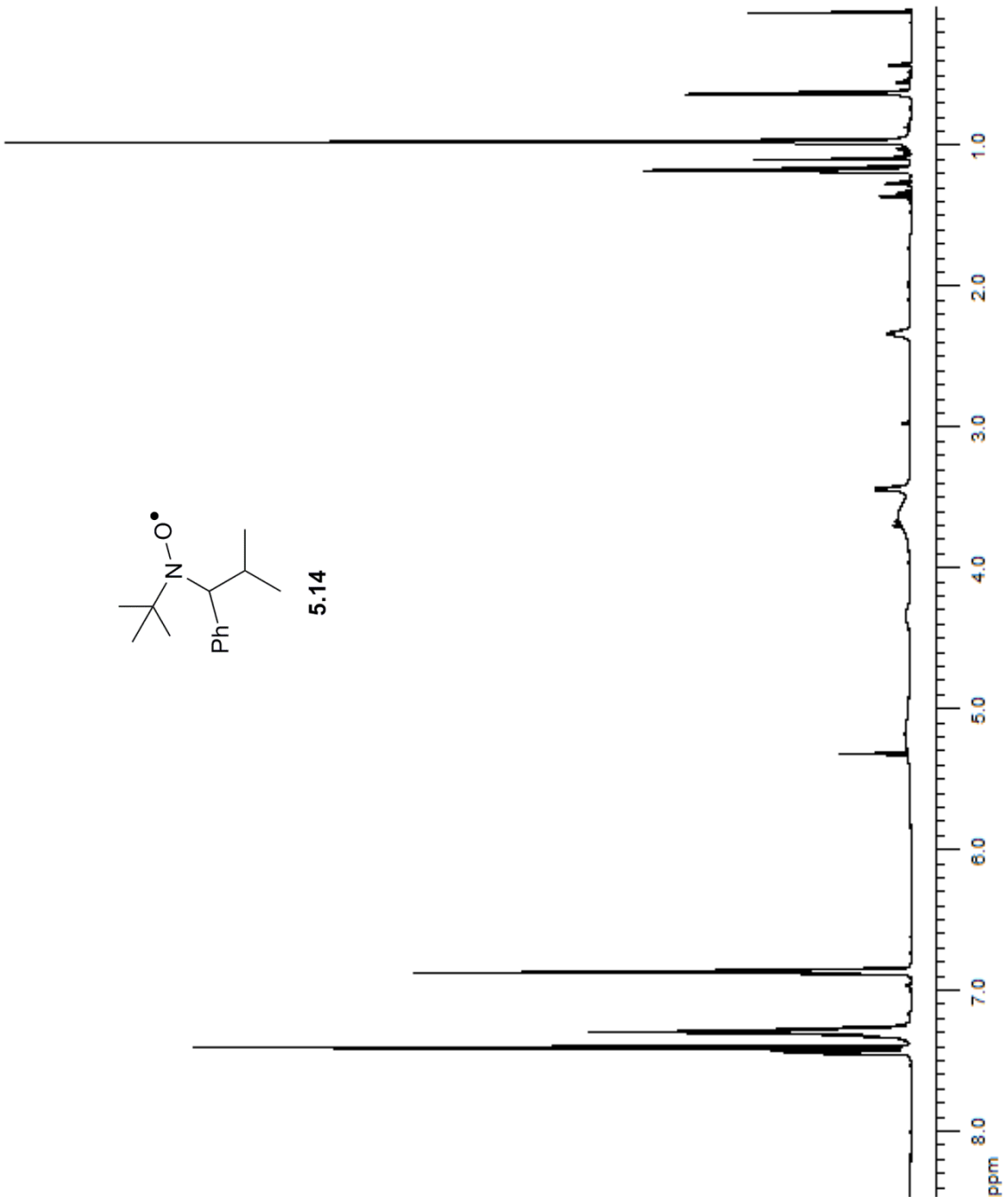

N
O
OH
4.143
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm


N
O
OH

4.143


CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm


5.13
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm


O
N
Ph
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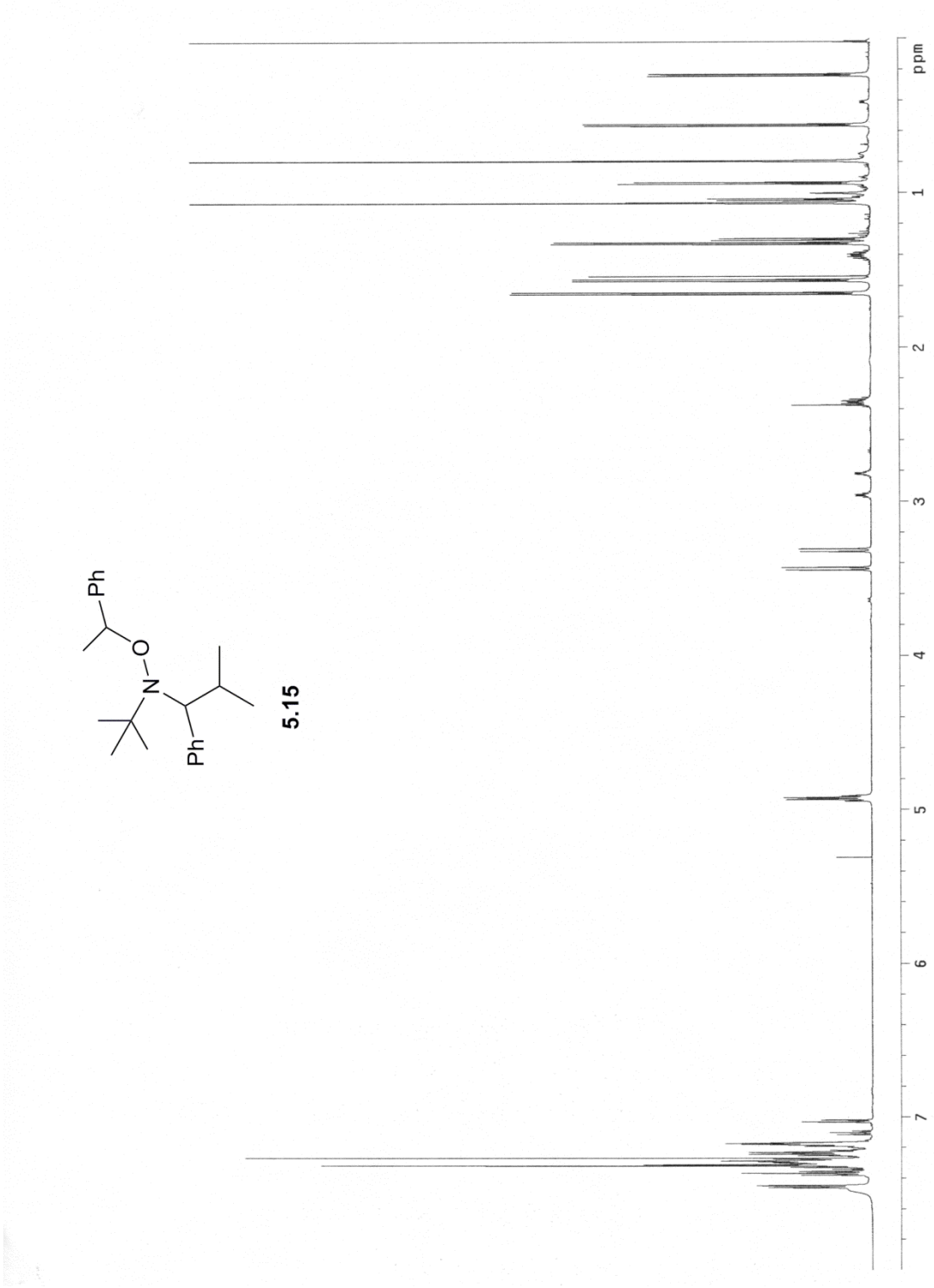
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm


Ph
O
N
Ph
5.15
ppm
1
2
3
4
5
6
7


Ph
Ph
n
Ph
O
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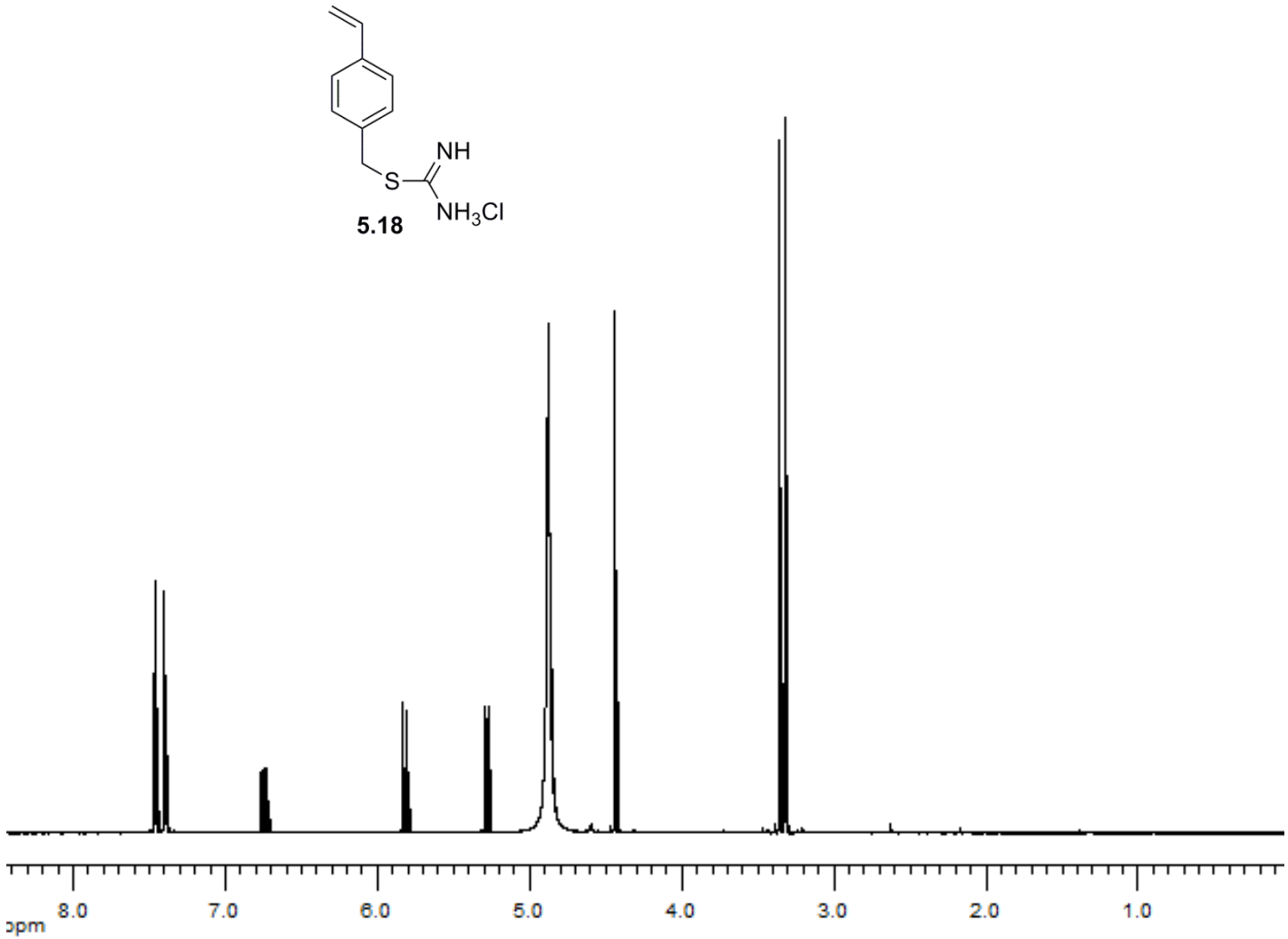
Ph
ppm
1
2
3
4
5
6
7

5.17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S
NH3Cl
5.18
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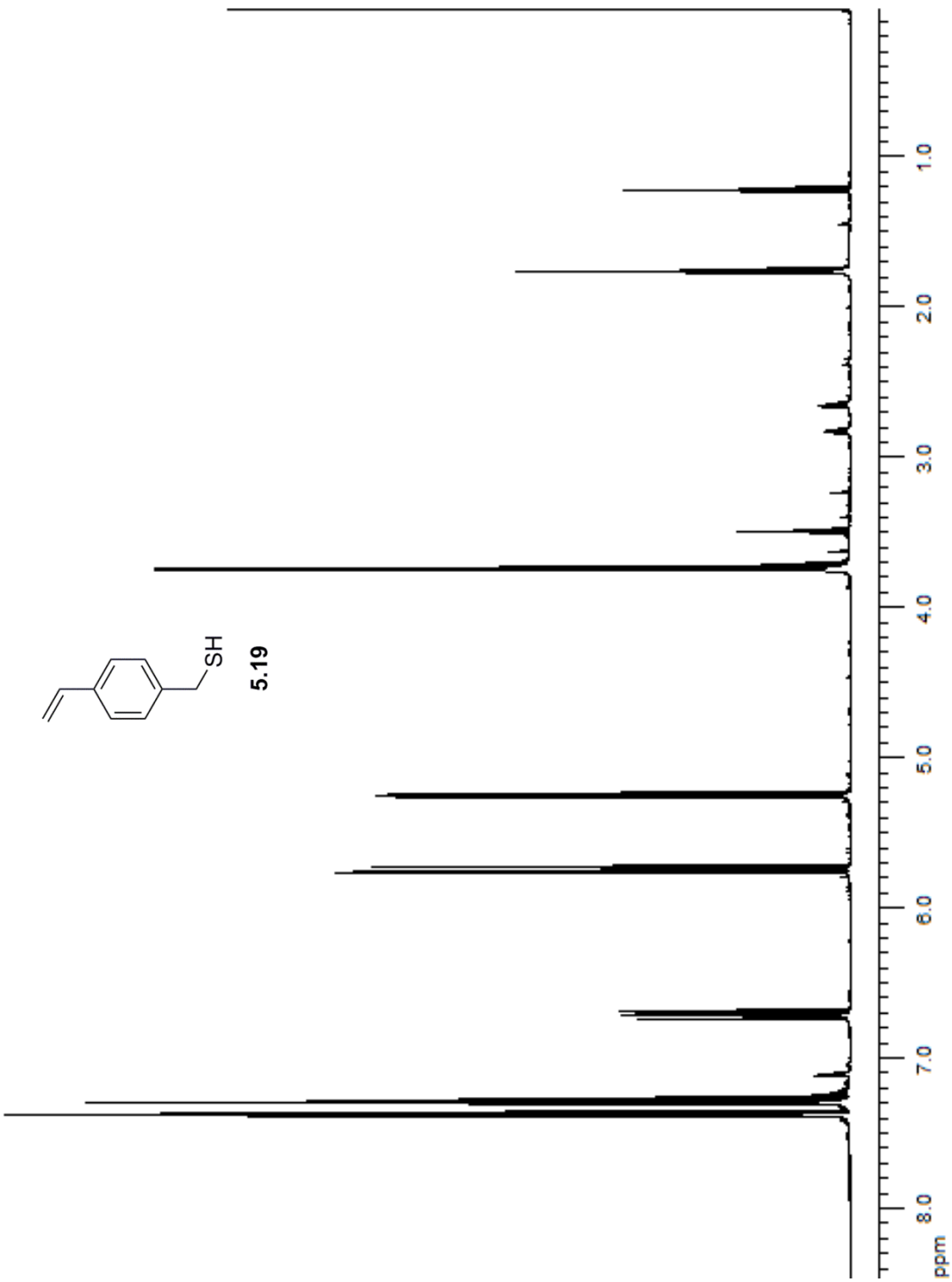
6.0
5.0
4.0
3.0
2.0
1.0
ppm


SH
5.19
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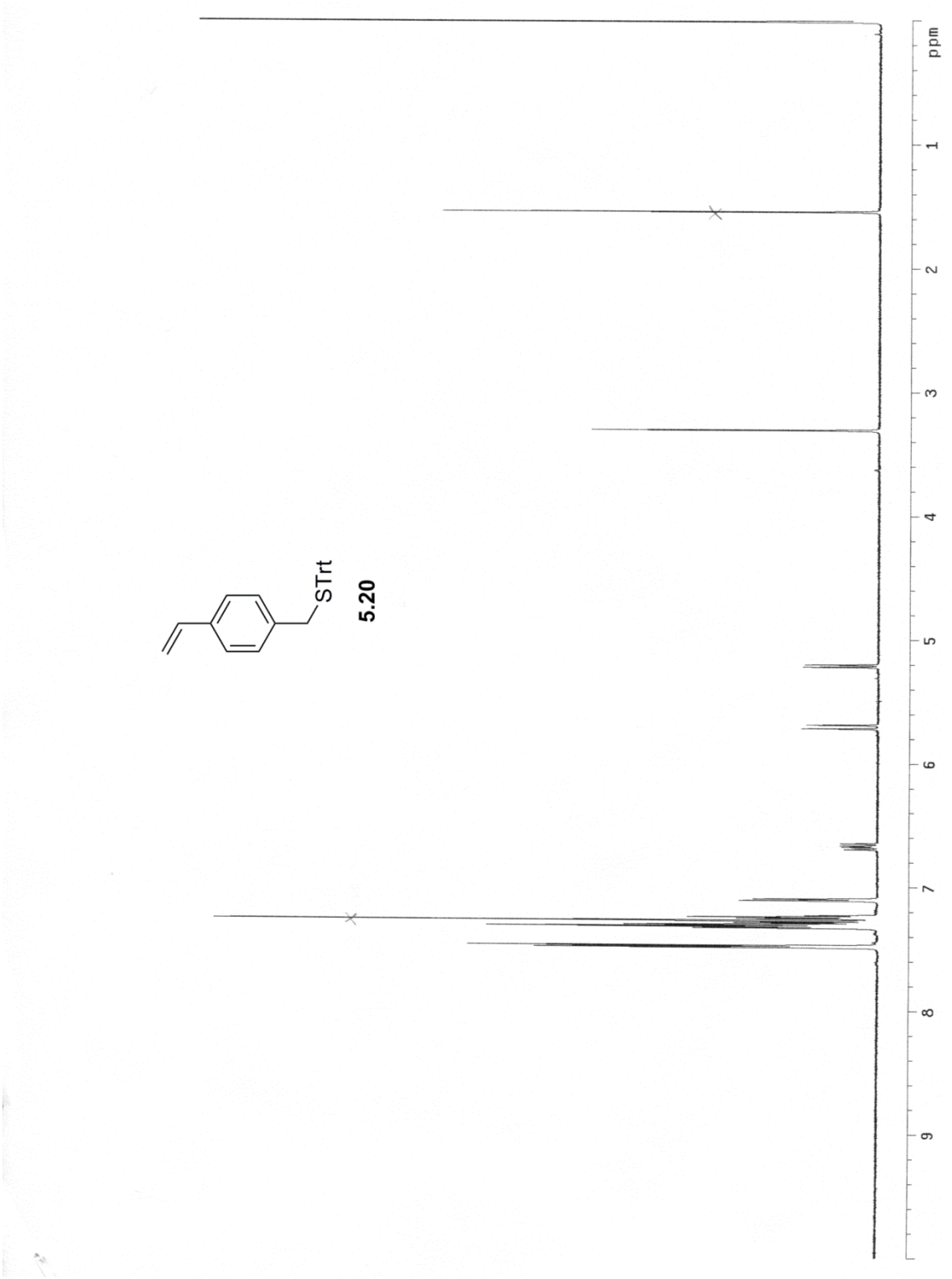
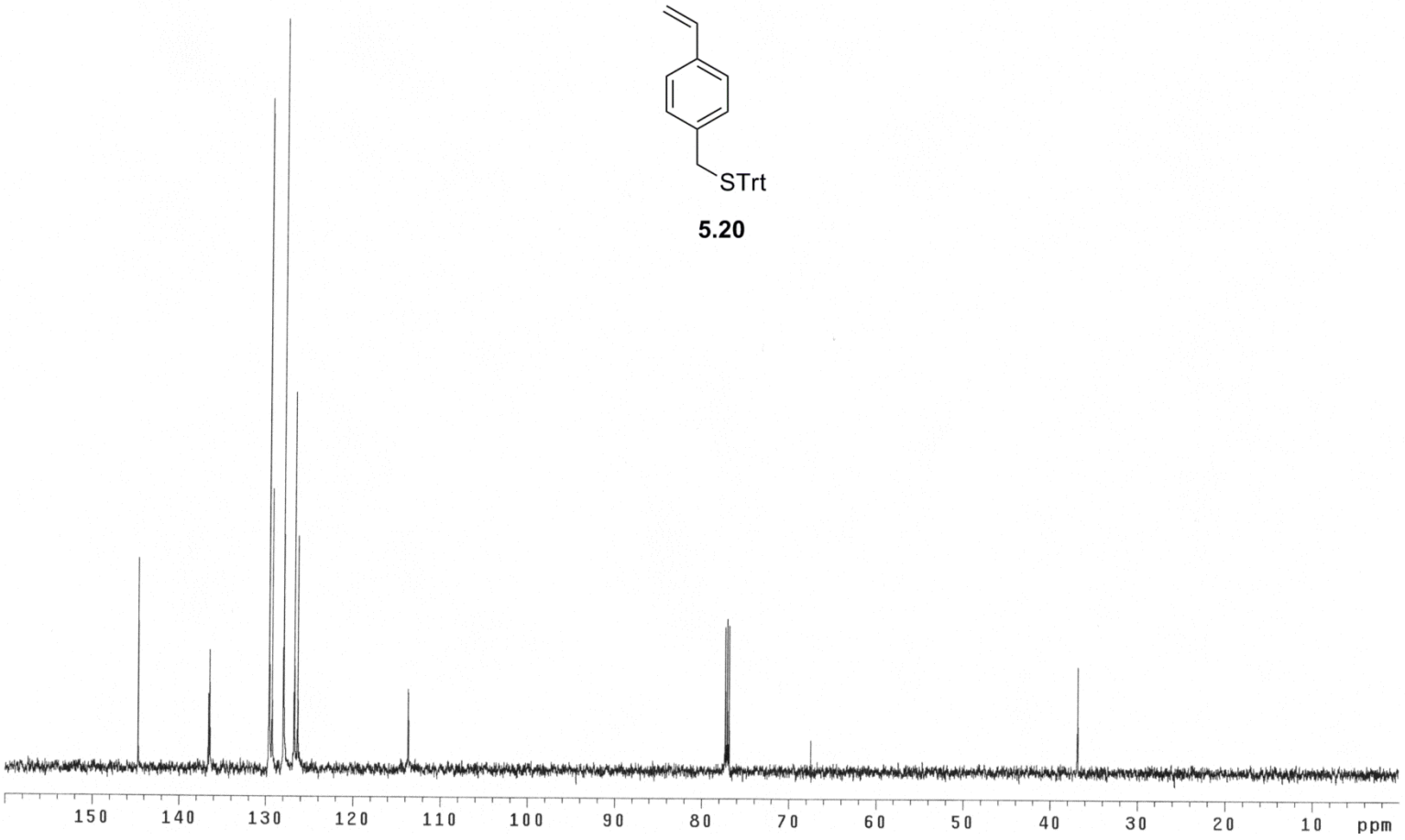
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm


STrt
5.20
ppm
1
2
3
4
5
6
7
8
9



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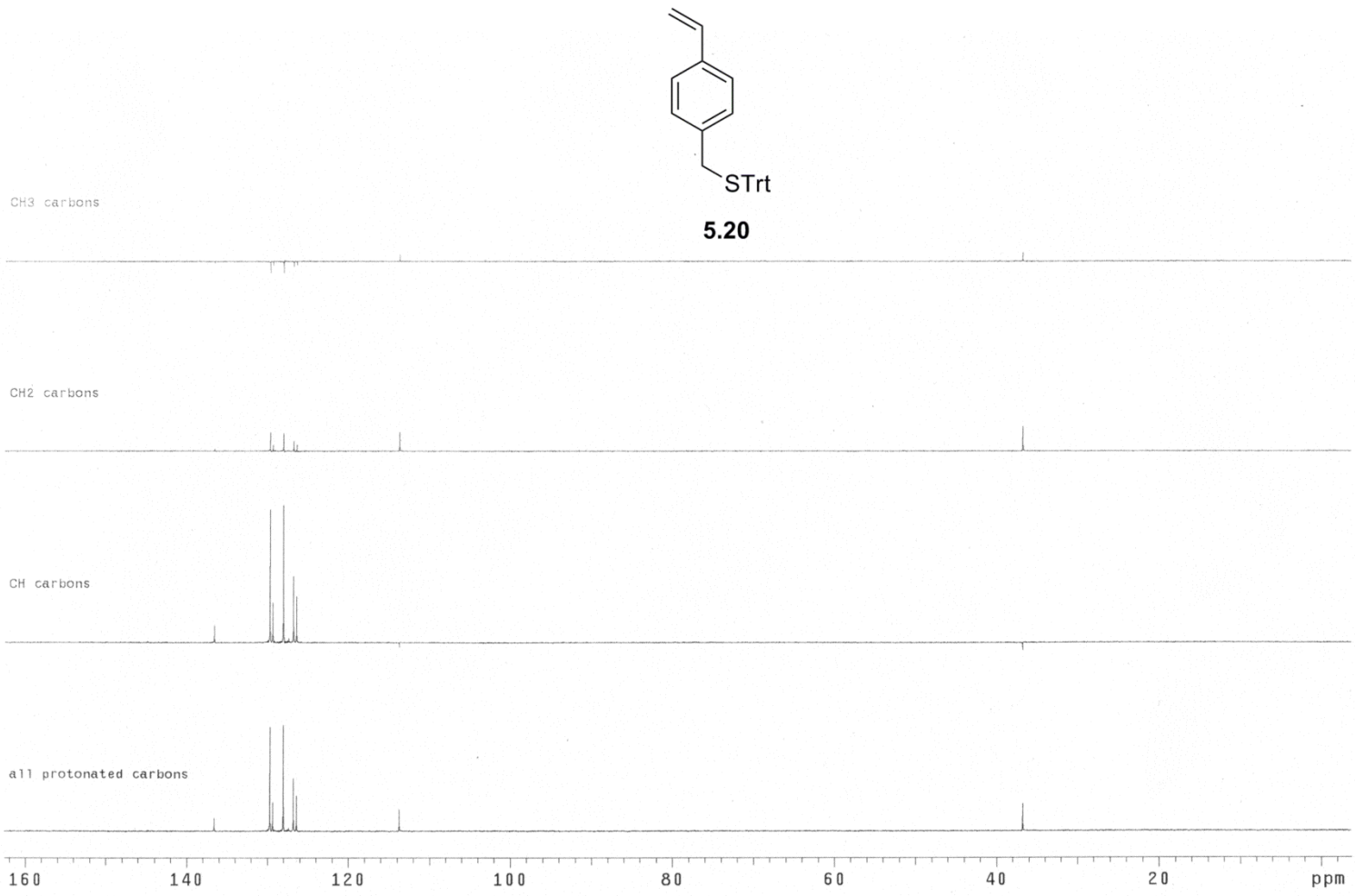
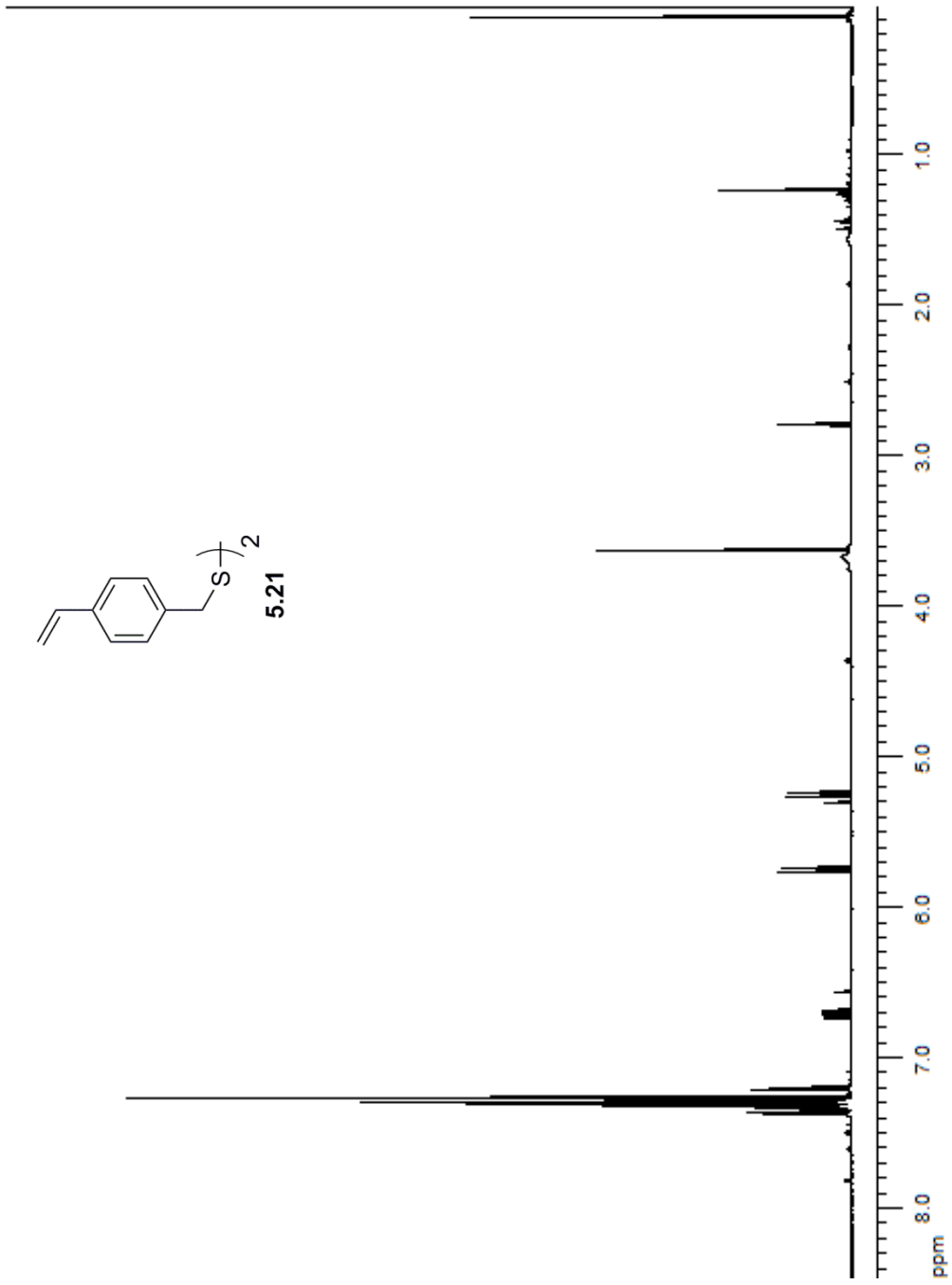
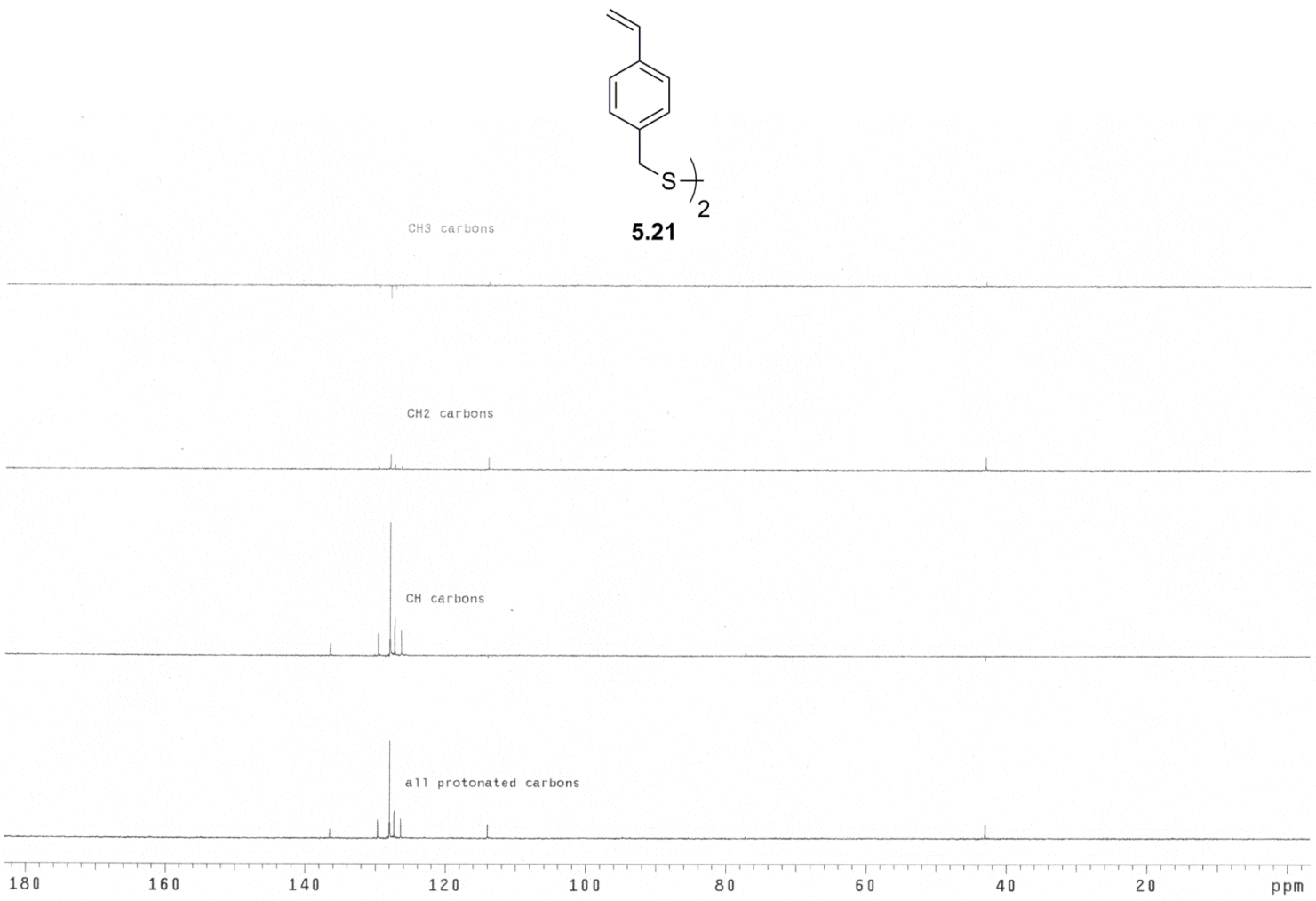
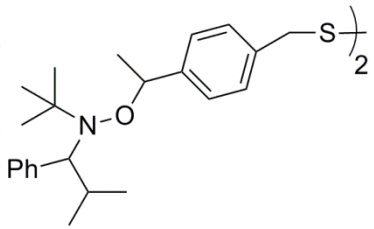

STrt
5.20
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
160
140
120
100
80
60
40
20
ppm


S
2
5.21
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm

S
2
5.21
ppm
20
40
60
80
100
120
140
160


S
2
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm

5.21



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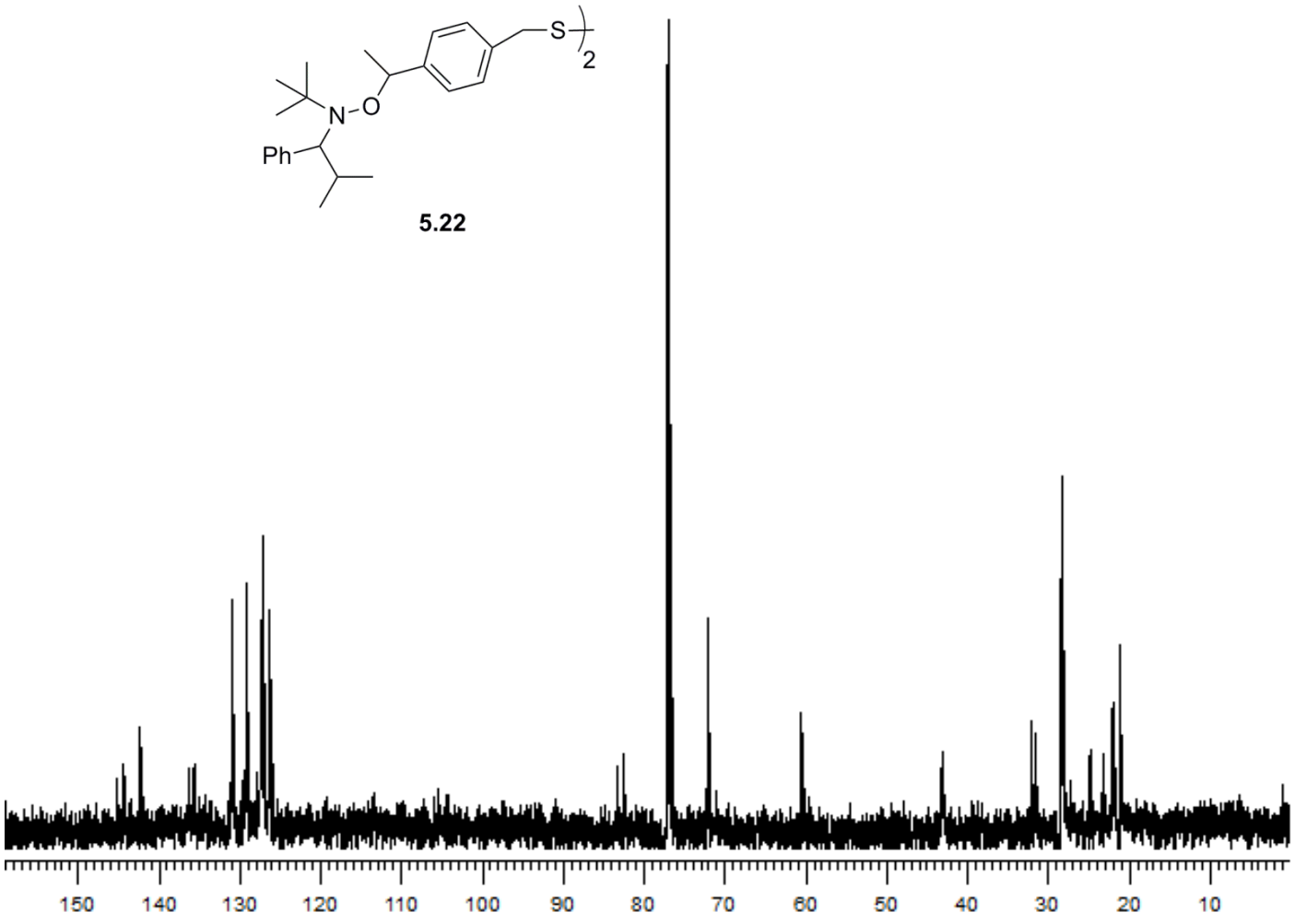

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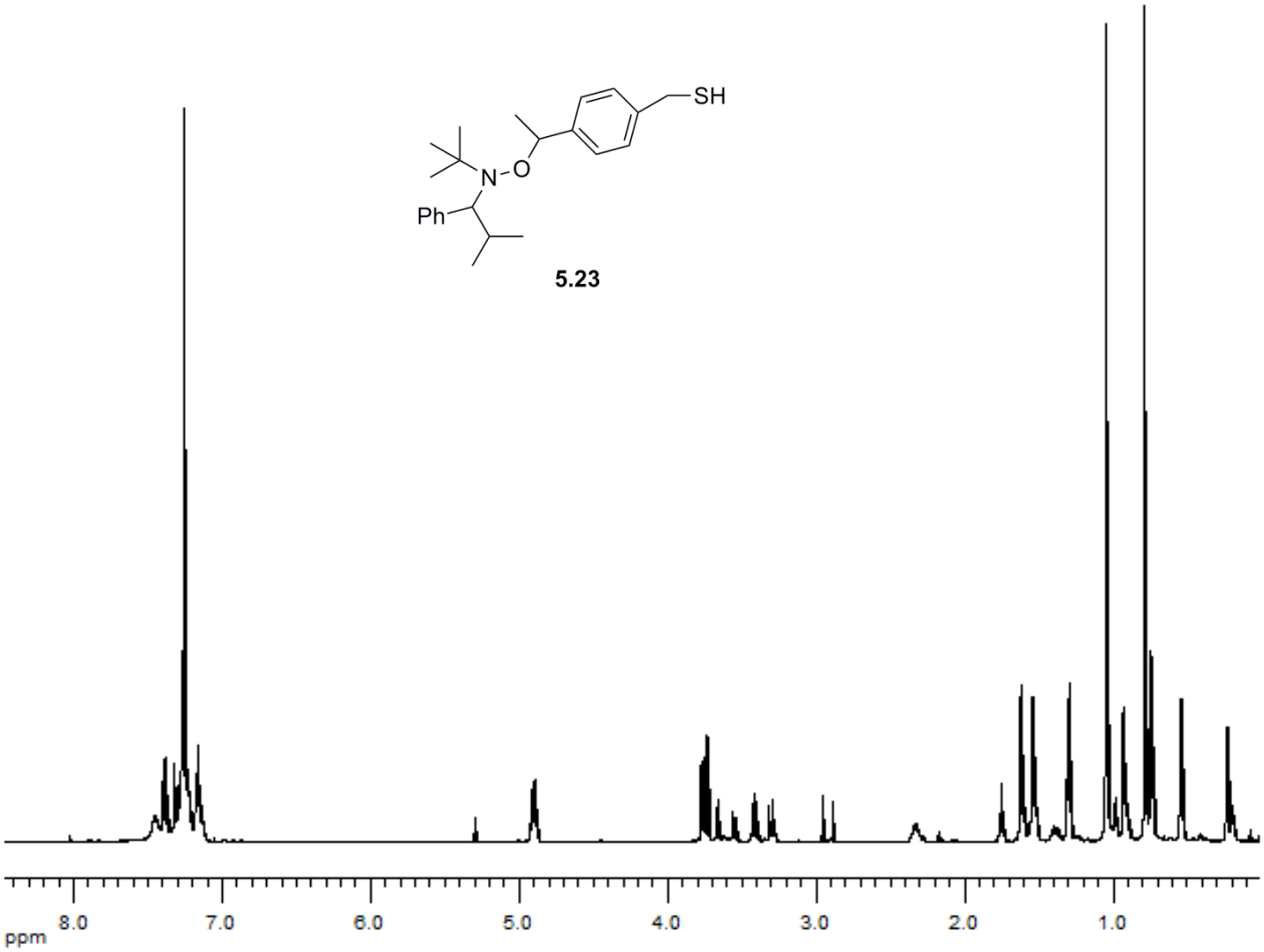

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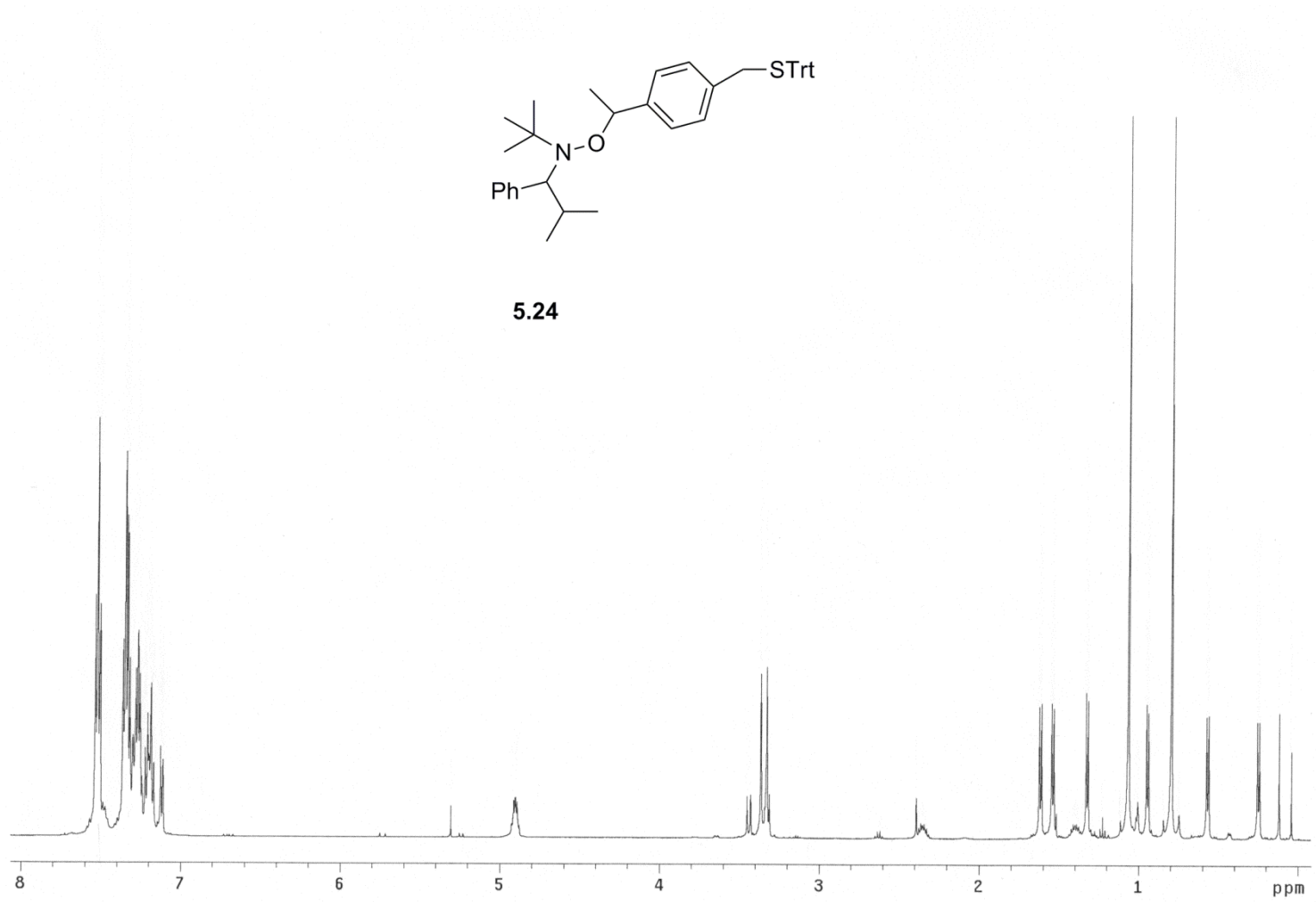

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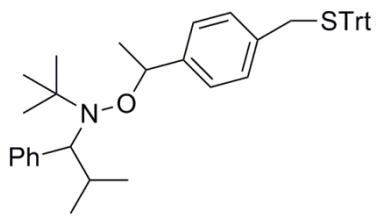

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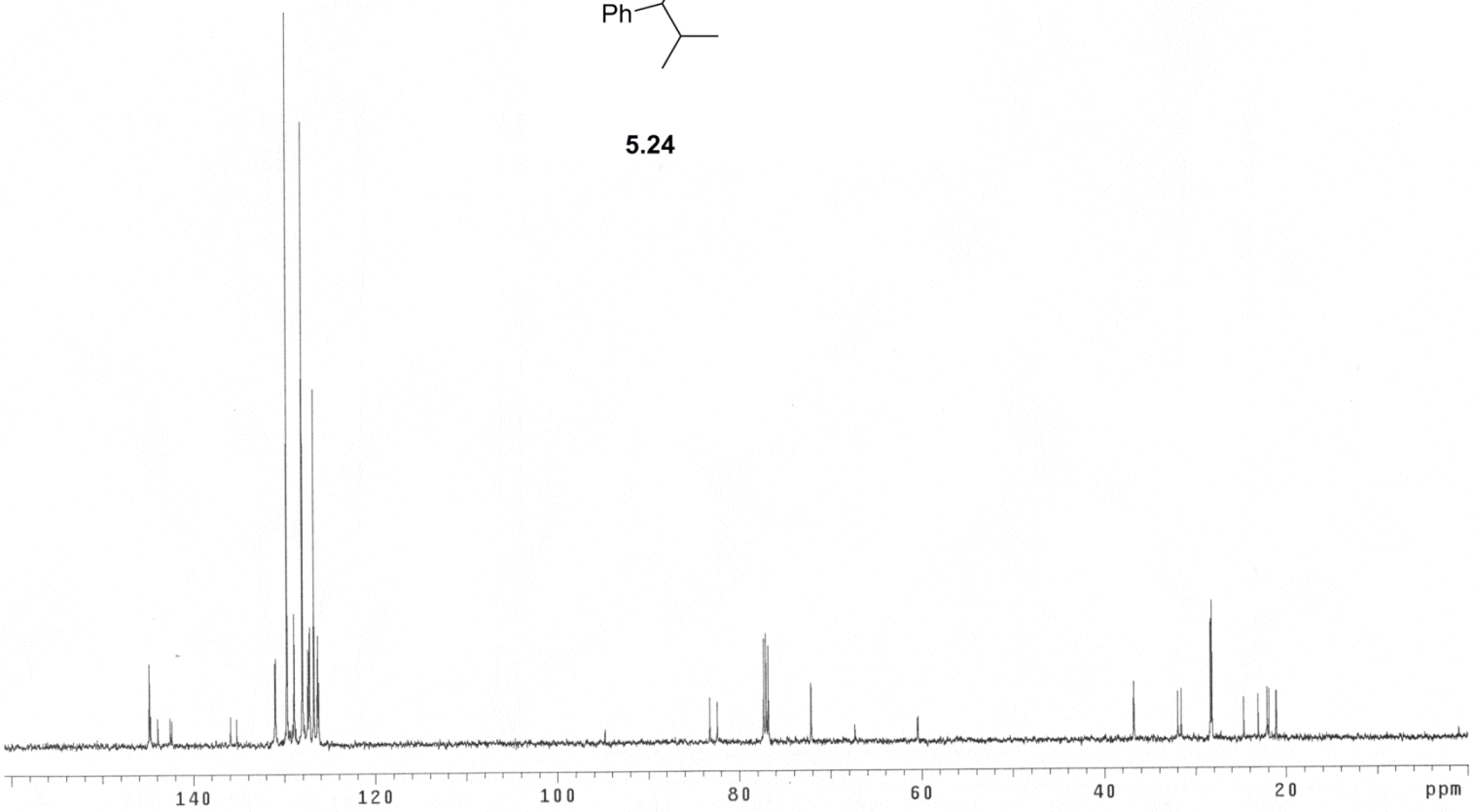

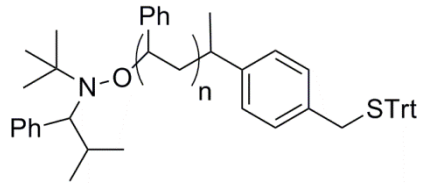

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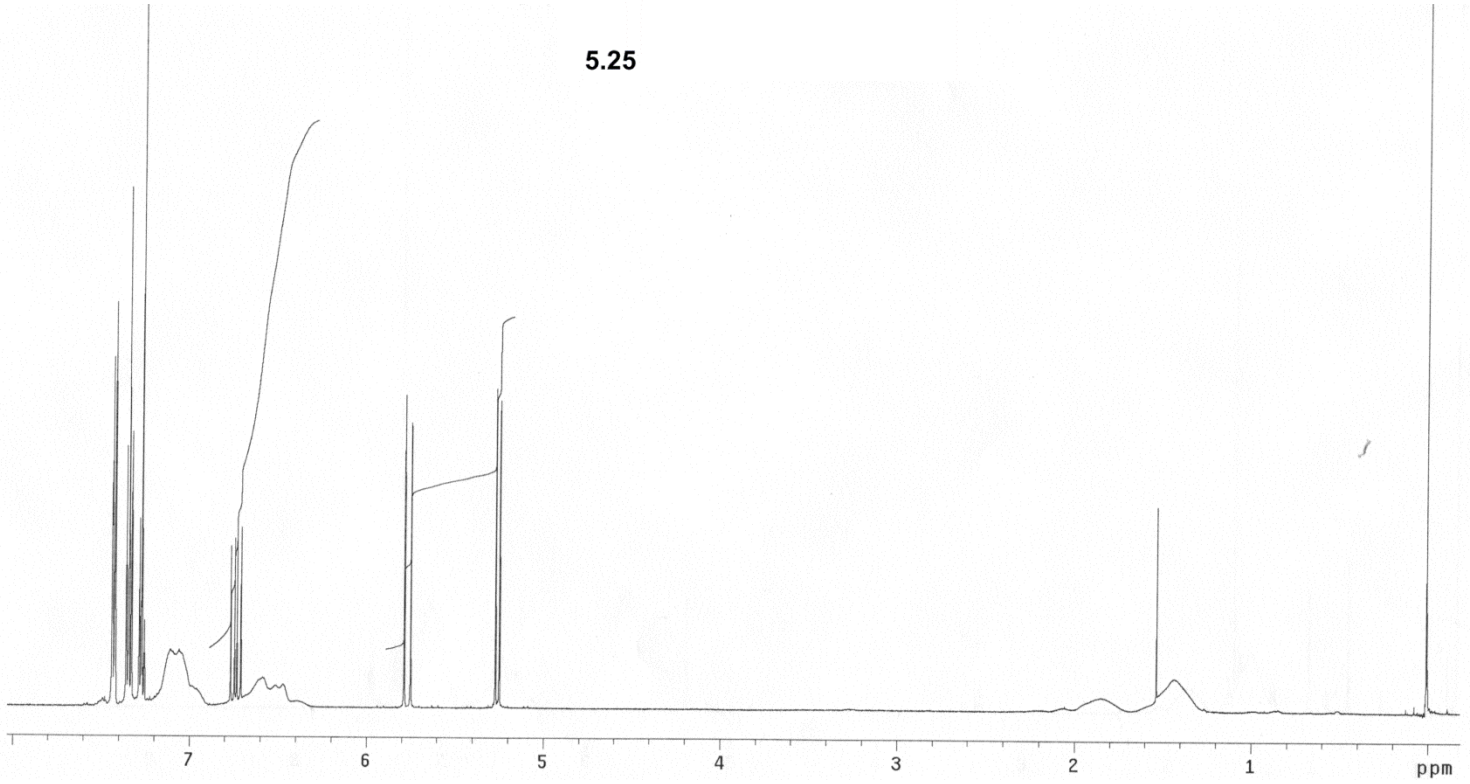

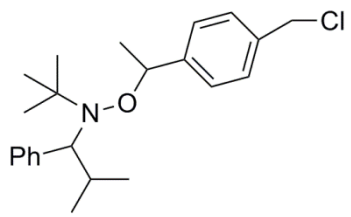

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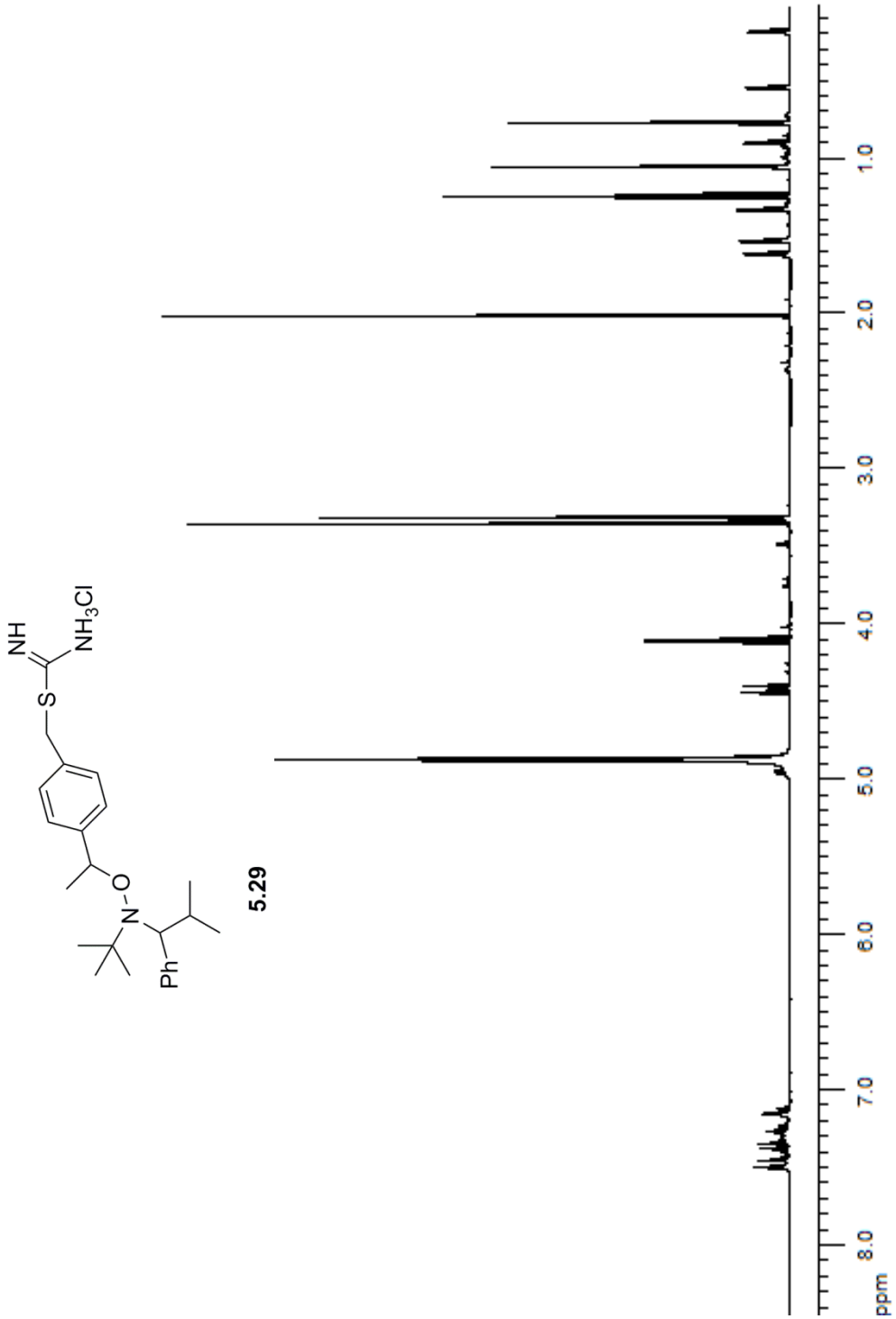
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NH3Cl
S
N
O
Ph
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3.0
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ppm

Bibliography

Abrams, F. S.; London, E., *Biochemistry* **1993,** *32* (40), 10826-10831.

Acharya, H. P.; Miyoshi, K.; Kobayashi, Y., *Organic Letters* **2007,** *9* (18), 3535-3538.

Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A., *Chemical Reviews* **2001,** *101* (11), 3499-3548.

Adegoke, O.; Hosten, E.; McCleland, C.; Nyokong, T., *Analytica Chimica Acta* **2012,** *721*, 154-161.

Adorjan, I.; Jaaskelainen, A. S.; Vuorinen, T., *Carbohydrate Research* **2006,** *341* (14), 2439-2443.

Ahn, H.-Y.; Fairfull-Smith, K. E.; Morrow, B. J.; Lussini, V.; Kim, B.; Bondar, M. V.; Bottle, S. E.; Belfield, K. D., *Journal of the American Chemical Society* **2012,** *134* (10), 4721-4730.

Ahrens, B.; Davidson, M. G.; Forsyth, V. T.; Mahon, M. F.; Johnson, A. L.; Mason, S. A.; Price, R. D.; Raithby, P. R., *Journal of the American Chemical Society* **2001,** *123* (37), 9164-9165.

Alaghmand, M.; Blough, N. V., *Environmental Science & Technology* **2007,** *41* (7), 2364-2370.

Alamsetti, S. K.; Mannam, S.; Mutupandi, P.; Sekar, G., *Chemistry-A European Journal* **2009,** *15* (5), 1086-1090.

Aldana, J.; Lavelle, N.; Wang, Y. J.; Peng, X. G., *Journal of the American Chemical Society* **2005,** *127* (8), 2496-2504.

Aliaga, C.; Aspée, A.; Scaiano, J. C., *Organic Letters* **2003,** *5* (22), 4145-4148.

Aliaga, C.; Juarez-Ruiz, J. M.; Scaiano, J. C.; Aspee, A., *Organic Letters* **2008,** *10* (11), 2147-2150.

Aliaga, C.; Rezende, M. C.; Tirapegui, C., *Tetrahedron* **2009,** *65* (31), 6025-6028.

Alivisatos, A. P., *Journal of Physical Chemistry* **1996,** *100* (31), 13226-13239.

Alivisatos, A. P., *Science* **1996,** *271* (5251), 933-937.

Ananchenko, G. S.; Fischer, H., *Journal of Polymer Science Part a-Polymer Chemistry* **2001,** *39* (20), 3604-3621.

Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S., *Journal of Organic Chemistry* **1989,** *54* (12), 2970-2972.

Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S., *Journal of Organic Chemistry* **1987,** *52* (12), 2559-2562.

Annunziatini, C.; Gerini, M. F.; Lanzalunga, O.; Lucarini, M., *Journal of Organic Chemistry* **2004,** *69* (10), 3431-3438.

Anraku, Y.; Takahashi, Y.; Kitano, H.; Hakari, M., *Colloids and Surfaces B-Biointerfaces* **2007,** *57* (1), 61-68.

Appelt, M.; Schmidt-Naake, G., *Macromolecular Materials and Engineering* **2004,** *289* (3), 245-253.

Arends, I.; Li, Y. X.; Ausan, R.; Sheldon, R. A., *Tetrahedron* **2006,** *62* (28), 6659-6665.

Arends, I.; Li, Y. X.; Sheldon, R. A., *Biocatalysis and Biotransformation* **2006,** *24* (6), 443-448.

Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocienski, P.; Pimm, A.; Bell, R., *Synthesis-Stuttgart* **1995,** (2), 199-206.

Aspée, A.; Allaga, C.; Scaiano, J. C., *Photochemistry and Photobiology* **2007,** *83* (3), 481-485.

Aspée, A.; Garcia, O.; Maretti, L.; Sastre, R.; Scaiano, J. C., *Macromolecules* **2003,** *36* (10), 3550-3556.

Aspee, A.; Maretti, L.; Scaiano, J. C., *Photochemical & Photobiological Sciences* **2003,** *2* (11), 1125-1129.

Aspée, A.; Orrego, A.; Alarcón, E.; López-Alarcón, C.; Poblete, H.; Gónzalez-Nilo, D., *Bioorganic & Medicinal Chemistry Letters* **2009,** *19* (22), 6382-6385.

Asuncionpunzalan, E.; London, E., *Biochemistry* **1995,** *34* (36), 11460-11466.

Azzena, U.; Pisano, L.; Mocci, S., *Journal of Organometallic Chemistry* **2009,** *694* (22), 3619-3625.

Babiarz, J. E.; Cunkle, G. T.; DeBellis, A. D.; Eveland, D.; Pastor, S. D.; Shum, S. P., *Journal of Organic Chemistry* **2002,** *67* (19), 6831-6834.

Baciocchi, E.; Calcagni, A.; Lanzalunga, O., *Journal of Organic Chemistry* **2008,** *73* (11), 4110-4115.

Bae, S. K.; Lee, S. Y.; Hong, S. C., *Reactive & Functional Polymers* **2011,** *71* (2), 187-194.

Bahri, M. A.; Heyne, B. J.; Hans, P.; Seret, A. E.; Mouithys-Mickalad, A. A.; Hoebeke, M. D., *Biophysical Chemistry* **2005,** *114* (1), 53-61.

Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B., *Journal of Organic Chemistry* **2007,** *72* (12), 4504-4509.

Ballesteros, O. G.; Maretti, L.; Sastre, R.; Scaiano, J. C., *Macromolecules* **2001,** *34* (18), 6184-6187.

Banerjee, S.; Kar, S.; Perez, J. M.; Santra, S., *Journal of Physical Chemistry C* **2009,** *113* (22), 9659-9663.

Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M., *Journal of Organic Chemistry* **1994,** *59* (21), 6338-6343.

Bapat, J. B.; Black, D. S. C., *Australian Journal of Chemistry* **1968,** *21* (10), 2483-2495.

Baracz, N. M.; Hankovszky, O. H.; Sar, C. P.; Jerkovich, G.; Hideg, K., *Synthesis-Stuttgart* **1996,** (2), 204-208.

Barhate, N.; Cekan, P.; Massey, A. P.; Sigurdsson, S. T., *Angewandte Chemie-International Edition* **2007,** *46* (15), 2655-2658.

Barhdadi, R.; Comminges, C.; Doherty, A. P.; Nedelec, J. Y.; O'Toole, S.; Troupel, M., *Journal of Applied Electrochemistry* **2007,** *37* (6), 723-728.

Bartalis, J.; Chan, W. G.; Wooten, J. B., *Analytical Chemistry* **2007,** *79* (13), 5103-5106.

Bartalis, J.; Zhao, Y. L.; Flora, J. W.; Paine, J. B.; Wooten, J. B., *Analytical Chemistry* **2009,** *81* (2), 631-641.

Barton, D. H. R.; Crich, D.; Kretzschmar, G., *Journal of the Chemical Society-Perkin Transactions 1* **1986,** (1), 39-53.

Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Journal of the Chemical Society-Chemical Communications* **1983,** (17), 939-941.

Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Tetrahedron* **1985,** *41* (19), 3901-3924.

Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Tetrahedron Letters* **1983,** *24* (45), 4979-4982.

Barton, D. H. R.; Crich, D.; Potier, P., *Tetrahedron Letters* **1985,** *26* (48), 5943-5946.

Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A., *Tetrahedron* **1992,** *48* (13), 2613-2626.

Barton, D. H. R.; Lacher, B.; Zard, S. Z., *Tetrahedron Letters* **1985,** *26* (48), 5939-5942.

Barton, D. H. R.; Ozbalik, N.; Vacher, B., *Tetrahedron* **1988,** *44* (12), 3501-3512.

Batz, M.; Korth, H. G.; Sustmann, R., *Angewandte Chemie-International Edition in English* **1997,** *36* (13-14), 1501-1503.

Baucherel, X.; Arends, I.; Ellwood, S.; Sheldon, R. A., *Organic Process Research & Development* **2003,** *7* (3), 426-428.

Baucherel, X.; Gonsalvi, L.; Arends, I.; Ellwood, S.; Sheldon, R. A., *Advanced Synthesis & Catalysis* **2004,** *346* (2-3), 286-296.

Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U., *Journal of the American Chemical Society* **1992,** *114* (13), 4983-4992.

Behrendt, J. M.; Afzaal, M.; Alexander, L. M.; Bradley, M.; Hine, A. V.; Nagel, D.; O'Brien, P.; Presland, K.; Sutherland, A. J., *Journal of Materials Chemistry* **2009,** *19* (2), 215-221.

Benaglia, M.; Puglisi, A.; Holczknecht, O.; Quici, S.; Pozzi, G., *Tetrahedron* **2005,** *61* (51), 12058-12064.

Ben-Daniel, R.; Alsters, P.; Neumann, R., *Journal of Organic Chemistry* **2001,** *66* (25), 8650-8653.

Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J., *Journal of the American Chemical Society* **1999,** *121* (16), 3904-3920.

Benoit, D.; Harth, E.; Fox, P.; Waymouth, R. M.; Hawker, C. J., *Macromolecules* **2000,** *33* (2), 363-370.

Besson, T.; Coudert, G.; Guillaumet, G., *Journal of Heterocyclic Chemistry* **1991,** *28* (6), 1517-1523.

Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P., *Tetrahedron Letters* **2000,** *41* (22), 4343-4346.

Bian, Z. Y.; Guo, X. Q.; Zhao, Y. B.; Du, J. O., *Analytical Sciences* **2005,** *21* (5), 553-559.

Billone, P. S.; Maretti, L.; Maurel, V.; Scaiano, J. C., *Journal of the American Chemical Society* **2007,** *129* (46), 14150-14151.

Bisht, H. S.; Chatterjee, A. K., *Journal of Macromolecular Science-Polymer Reviews* **2001,** *C41* (3), 139-173.

Blinco, J. P.; Fairfull-Smith, K. E.; Micaller, A. S.; Bottle, S. E., *Polymer Chemistry* **2010,** *1* (7), 1009-1012.

Blinco, J. P.; Fairfull-Smith, K. E.; Morrow, B. J.; Bottle, S. E., *Australian Journal of Chemistry* **2011,** *64* (4), 373-389.

Blinco, J. P.; Keddie, D. J.; Wade, T.; Barker, P. J.; George, G. A.; Bottle, S. E., *Polymer Degradation and Stability* **2008,** *93* (9), 1613-1618.

Blinco, J. P.; McMurtrie, J. C.; Bottle, S. E., *European Journal of Organic Chemistry* **2007,** (28), 4638-4641.

Blough, N. V.; Simpson, D. J., *Journal of the American Chemical Society* **1988,** *110* (6), 1915-1917.

Boaz, H.; Rollefson, G. K., *Journal of the American Chemical Society* **1950,** *72* (8), 3435-3443.

Bobbitt, J. M., *Journal of Organic Chemistry* **1998,** *63* (25), 9367-9374.

Bobbitt, J. M., *Molecules* **1999,** *4* (9), M102.

Bobbitt, J. M.; Flores, M. C. L., *Heterocycles* **1988,** *27* (2), 509-533.

Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z. K.; Tang, H. T., *Heterocycles* **1990,** *30* (2), 1131-1140.

Boeckman, R. K.; Shao, P.; Mullins, J. J., *Organic Syntheses* **2000,** *77*, 141.

Boger, D. L.; Cassidy, K. C.; Nakahara, S., *Journal of the American Chemical Society* **1993,** *115* (23), 10733-10741.

Bognar, B.; Jeko, J.; Kalai, T.; Hideg, K., *Dyes and Pigments* **2010,** *87* (3), 218-224.

Bognar, B.; Osz, E.; Hideg, K.; Kalai, T., *Journal of Heterocyclic Chemistry* **2006,** *43* (1), 81-86.

Bolm, C.; Fey, T., *Chemical Communications* **1999,** (18), 1795-1796.

Bolm, C.; Magnus, A. S.; Hildebrand, J. P., *Organic Letters* **2000,** *2* (8), 1173-1175.

Borisenko, G. G.; Martin, I.; Zhao, Q.; Amoscato, A. A.; Tyurina, Y. Y.; Kagan, V. E., *Journal of Biological Chemistry* **2004,** *279* (22), 23453-23462.

Borisenko, G. G.; Martin, I.; Zhao, Q.; Amoscato, A.; Kagan, V. E., *Journal of the American Chemical Society* **2004,** *126* (30), 9221-9232.

Bottle, S. E.; Busfield, W. K.; Jenkins, I. D., *Journal of the Chemical Society-Perkin Transactions 2* **1992,** (12), 2145-2150.

Bottle, S. E.; Chand, U.; Micallef, A. S., *Chemistry Letters* **1997,** (9), 857-858.

Bourbonnais, R.; Paice, M. G., *Febs Letters* **1990,** *267* (1), 99-102.

Bragd, P. L.; van Bekkum, H.; Besemer, A. C., *Topics in Catalysis* **2004,** *27* (1-4), 49-66.

Breton, T.; Bashiardes, G.; Leger, J. M.; Kokoh, K. B., *European Journal of Organic Chemistry* **2007,** (10), 1567-1570.

Breton, T.; Liaigre, D.; Belgsir, E., *Tetrahedron Letters* **2005,** *46* (14), 2487-2490.

Brunel, D.; Fajula, F.; Nagy, J. B.; Deroide, B.; Verhoef, M. J.; Veum, L.; Peters, J. A.; van Bekkum, H., *Applied Catalysis A-General* **2001,** *213* (1), 73-82.

Brunjes, M.; Sourkouni-Argirusi, G.; Kirschning, A., *Advanced Synthesis & Catalysis* **2003,** *345* (5), 635-642.

Bueno, C.; Mikelsons, L.; Maretti, L.; Scaiano, J. C.; Aspée, A., *Photochemistry and Photobiology* **2008,** *84* (6), 1535-1542.

Buhrmester, C.; Moshurchak, L. M.; Wang, R. L.; Dahn, J. R., *Journal of the Electrochemical Society* **2006,** *153* (10), A1800-A1804.

Bushmakina, N. G.; Misharin, A. Y., *Synthesis-Stuttgart* **1986,** (11), 966-966.

But, T. Y. S.; Tashino, Y.; Togo, H.; Toy, P. H., *Organic & Biomolecular Chemistry* **2005,** *3* (6), 970-971.

Callan, J. F.; Mulrooney, R. C.; Kamila, S.; McCaughan, B., *Journal of Fluorescence* **2008,** *18* (2), 527-532.

Caneschi, A.; Gatteschi, D.; Sessoli, R.; Rey, P., *Accounts of Chemical Research* **1989,** *22* (11), 392-398.

Carland, M. W.; Martin, R. L.; Schiesser, C. H., *Organic & Biomolecular Chemistry* **2004,** *2* (18), 2612-2618.

Castro, B.; Selve, C., *Bulletin De La Societe Chimique De France* **1971,** (6), 2296-2298.

Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F., *Tetrahedron Letters* **2001,** *42* (38), 6651-6653.

Cekan, P.; Smith, A. L.; Barhate, N.; Robinson, B. H.; Sigurdsson, S. T., *Nucleic Acids Research* **2008,** *36* (18), 5946-5954.

Cella, J. A.; Kelley, J. A.; Kenehan, E. F., *Journal of Organic Chemistry* **1975,** *40* (12), 1860-1862.

Chang, E.; Miller, J. S.; Sun, J. T.; Yu, W. W.; Colvin, V. L.; Drezek, R.; West, J. L., *Biochemical and Biophysical Research Communications* **2005,** *334* (4), 1317-1321.

Chattopadhyay, S. K.; Das, P. K.; Hug, G. L., *Journal of the American Chemical Society* **1983,** *105* (20), 6205-6210.

Chaudhari, S. S.; Akamanchi, K. G., *Synlett* **1999,** (11), 1763-1765.

Chechik, V.; Wellsted, H. J.; Korte, A.; Gilbert, B. C.; Caldararu, H.; Ionita, P.; Caragheorgheopol, A., *Faraday Discussions* **2004,** *125*, 279-291.

Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C., *Journal of the American Chemical Society* **2005,** *127* (19), 6970-6971.

Chen, W. B.; Wang, X.; Tu, X. J.; Pei, D. J.; Zhao, Y.; Guo, X. Q., *Small* **2008,** *4* (6), 759-764.

Chen, Y. S.; Wang, P. G., *Tetrahedron Letters* **2001,** *42* (30), 4955-4958.

Cho, C. H.; Kim, S., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2005,** *83* (6-7), 917-921.

Cho, N. S.; Park, C. H., *Bulletin of the Korean Chemical Society* **1994,** *15* (11), 924-926.

Choudary, B. M.; Kantam, M. L.; Bharathi, B.; Reddy, C. R. V., *Journal of Molecular Catalysis A-Chemical* **2001,** *168* (1-2), 69-73.

Chujo, Y.; Sada, K.; Naka, A.; Nomura, R.; Saegusa, T., *Macromolecules* **1993,** *26* (5), 883-887.

Chung, Y. C.; Chen, I. H.; Chen, C. J., *Biomaterials* **2008,** *29* (12), 1807-1816.

Ciriminna, R.; Blum, J.; Avnir, D.; Pagliaro, M., *Chemical Communications* **2000,** (15), 1441-1442.

Ciriminna, R.; Bolm, C.; Fey, T.; Pagliaro, M., *Advanced Synthesis & Catalysis* **2002,** *344* (2), 159-163.

Ciriminna, R.; Pagliaro, M., *Organic Process Research & Development* **2010,** *14* (1), 245-251.

Clark, J. H.; Miller, J. M.; So, K. H., *Journal of the Chemical Society-Perkin Transactions 1* **1978,** (9), 941-946.

Coe, S.; Woo, W. K.; Bawendi, M.; Bulovic, V., *Nature* **2002,** *420* (6917), 800-803.

Coenjarts, C.; Garcia, O.; Llauger, L.; Palfreyman, J.; Vinette, A. L.; Scaiano, J. C., *Journal of the American Chemical Society* **2003,** *125* (3), 620-621.

Columbus, L.; Hubbell, W. L., *Trends in Biochemical Sciences* **2002,** *27* (6), 288-295.

Colvin, V. L.; Schlamp, M. C.; Alivisatos, A. P., *Nature* **1994,** *370* (6488), 354-357.

Colwell, J. M.; Blinco, J. P.; Hulbert, C.; Fairfull-Smith, K. E.; Bottle, S. E., *Australian Journal of Chemistry* **2011,** *64* (4), 426-432.

Colwell, J. M.; Walker, J. R.; Blinco, J. P.; Micallef, A. S.; George, G. A.; Bottle, S. E., *Polymer Degradation and Stability* **2010,** *95* (10), 2101-2109.

Cordes, D. B.; Gamsey, S.; Singaram, B., *Angewandte Chemie-International Edition* **2006,** *45* (23), 3829-3832.

Coseri, S.; Ingold, K. U., *Organic Letters* **2004,** *6* (10), 1641-1643.

Cui, Y.; Gong, X. Q.; Zhu, S. J.; Li, Y. H.; Su, W. Y.; Yang, Q. H.; Chang, J., *Journal of Materials Chemistry* **2012,** *22* (2), 462-469.

d'Acunzo, F.; Baiocco, P.; Fabbrini, M.; Galli, C.; Gentili, P., *European Journal of Organic Chemistry* **2002,** (24), 4195-4201.

d'Acunzo, F.; Baiocco, P.; Fabbrini, M.; Galli, C.; Gentili, P., *New Journal of Chemistry* **2002,** *26* (12), 1791-1794.

Dalcanale, E.; Montanari, F., *Journal of Organic Chemistry* **1986,** *51* (4), 567-569.

Dang, Y. M.; Guo, X. Q., *Applied Spectroscopy* **2006,** *60* (2), 203-207.

Danko, M.; Chmela, T.; Hrdlovič, P., *Polymer Degradation and Stability* **2003,** *79* (2), 333-343.

Dao, J.; Benoit, D.; Hawker, C. J., *Journal of Polymer Science Part A-Polymer Chemistry* **1998,** *36* (12), 2161-2167.

Davis, N. J.; Flitsch, S. L., *Tetrahedron Letters* **1993,** *34* (7), 1181-1184.

De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A., *Journal of Organic Chemistry* **2003,** *68* (12), 4999-5001.

De Luca, L.; Giacomelli, G.; Porcheddu, A., *Organic Letters* **2001,** *3* (19), 3041-3043.

De, P.; Kumar, D. P.; Mondal, A. K.; Mandal, P. C.; Mukhopadhyay, S.; Banerjee, R., *Polyhedron* **2010,** *29* (4), 1358-1362.

Delpierre, G. R.; Lamchen, M., *Journal of the Chemical Society* **1963,** (OCT), 4693-4701.

DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G., *Journal of Organic Chemistry* **1997,** *62* (20), 6974-6977.

Demizu, Y.; Shiigi, H.; Oda, T.; Matsumura, Y.; Onomura, O., *Tetrahedron Letters* **2008,** *49* (1), 48-52.

deNooy, A. E. J.; Besemer, A. C.; Vanbekkum, H., *Recueil Des Travaux Chimiques Des Pays-Bas-Journal of the Royal Netherlands Chemical Society* **1994,** *113* (3), 165-166.

deNooy, A. E. J.; Besemer, A. C.; vanBekkum, H., *Synthesis-Stuttgart* **1996,** (10), 1153-1174.

Detsi, A.; Roussis, V.; Tsotinis, A.; Roussakis, C.; Calogeropoulou, T., *Synlett* **2005,** (20), 3131-3135.

Dijksman, A. E.; Arends, I.; Sheldon, R. A., *Chemical Communications* **2000,** (4), 271-272.

Dijksman, A.; Arends, I.; Sheldon, R. A., *Chemical Communications* **1999,** (16), 1591-1592.

Dijksman, A.; Arends, I.; Sheldon, R. A., *Organic & Biomolecular Chemistry* **2003,** *1* (18), 3232-3237.

Dijksman, A.; Arends, I.; Sheldon, R. A., *Synlett* **2001,** (1), 102-104.

Dijksman, A.; Marino-Gonzalez, A.; Payeras, A. M. I.; Arends, I.; Sheldon, R. A., *Journal of the American Chemical Society* **2001,** *123* (28), 6826-6833.

Diltemiz, S. E.; Say, R.; Buyuktiryaki, S.; Hur, D.; Denizli, A.; Ersoz, A., *Talanta* **2008,** *75* (4), 890-896.

Dobbs, A. P.; Jones, P.; Penny, M. J.; Rigby, S. E., *Tetrahedron* **2009,** *65* (27), 5271-5277.

Duppe, P. M.; Talbierski, P. M.; Hornig, F. S.; Rauen, U.; Korth, H. G.; Wille, T.; Boese, R.; Omlor, T.; de Groot, H.; Sustmann, R., *Chemistry-A European Journal* **2010,** *16* (36), 11121-11132.

Dyadyusha, L.; Yin, H.; Jaiswal, S.; Brown, T.; Baumberg, J. J.; Booy, F. P.; Melvin, T., *Chemical Communications* **2005,** (25), 3201-3203.

Eames, J.; Coumbarides, G. S.; Suggate, M. J.; Weerasooriya, N., *European Journal of Organic Chemistry* **2003,** (4), 634-641.

Einhorn, C.; Einhorn, J.; Marcadal-Abbadi, C.; Pierre, J. L., *Journal of Organic Chemistry* **1999,** *64* (12), 4542-4546.

Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L., *Journal of Organic Chemistry* **1996,** *61* (21), 7452-7454.

El-Sadek, M. S. A.; Kumar, J. R.; Babu, S. M., *Current Applied Physics* **2010,** *10* (1), 317-322.

Esker, J. L.; Newcomb, M., *Tetrahedron Letters* **1992,** *33* (40), 5913-5916.

Eychmuller, A.; Rogach, A. L., *Pure and Applied Chemistry* **2000,** *72* (1-2), 179-188.

Fabbrini, M.; Galli, C.; Gentili, P., *Journal of Molecular Catalysis B-Enzymatic* **2002,** *16* (5-6), 231-240.

Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D., *Tetrahedron Letters* **2001,** *42* (43), 7551-7553.

Fabregat, V.; Angeles Izquierdo, M.; Isabel Burguete, M.; Galindo, F.; Luis, S. V., *Inorganica Chimica Acta* **2012,** *381*, 212-217.

Fairfull-Smith, K. E.; Blinco, J. P.; Keddie, D. J.; George, G. A.; Bottle, S. E., *Macromolecules* **2008,** *41* (5), 1577-1580.

Fairfull-Smith, K. E.; Bottle, S. E., *European Journal of Organic Chemistry* **2008,** (32), 5391-5400.

Fairfull-Smith, K. E.; Brackmann, F.; Bottle, S. E., *European Journal of Organic Chemistry* **2009,** (12), 1902-1915.

Feng, C.-L.; Zhong, X.; Steinhart, M.; Caminade, A.-M.; Majoral, J.-P.; Knoll, W., *Advanced Materials* **2007,** *19* (15), 1933-1936.

Fenner, T.; Schiesser, C. H., *Molecules* **2004,** *9* (6), 472-479.

Fenner, T.; White, J. M.; Schiesser, C. H., *Organic & Biomolecular Chemistry* **2006,** *4* (3), 466-474.

Ferreira, P.; Hayes, W.; Phillips, E.; Rippon, D.; Tsang, S. C., *Green Chemistry* **2004,** *6* (7), 310-312.

Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C., *Applied Catalysis B-Environmental* **2005,** *61* (3-4), 206-211.

Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C.; Hayes, W., *Journal of Organic Chemistry* **2004,** *69* (20), 6851-6859.

Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C., *Journal of Organic Chemistry* **2001,** *66* (24), 8154-8159.

Figiel, P. J.; Leskela, M.; Repo, T., *Advanced Synthesis & Catalysis* **2007,** *349* (7), 1173-1179.

Flicker, T. M.; Green, S. A., *Analytical Chemistry* **1998,** *70* (9), 2008-2012.

Flicker, T. M.; Green, S. A., *Environmental Health Perspectives* **2001,** *109* (8), 765-771.

Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K., *Synthesis-Stuttgart* **2003,** (7), 1055-1064.

Formaggio, F.; Bonchio, M.; Crisma, M.; Peggion, C.; Mezzato, S.; Polese, A.; Barazza, A.; Antonello, S.; Maran, F.; Broxterman, Q. B.; Kaptein, B.; Kamphuis, J.; Vitale, R. M.; Saviano, M.; Benedetti, E.; Toniolo, C., *Chemistry-A European Journal* **2002,** *8* (1), 84-93.

Fukuda, O.; Sakaguchi, S.; Ishii, Y., *Advanced Synthesis & Catalysis* **2001,** *343* (8), 809-813.

Gadanyi, S.; Kalai, T.; Jeko, J.; Berente, Z.; Hideg, K., *Synthesis-Stuttgart* **2000,** (14), 2039-2046.

Gamez, P.; Arends, I.; Reedijk, J.; Sheldon, R. A., *Chemical Communications* **2003,** (19), 2414-2415.

Gamez, P.; Arends, I.; Sheldon, R. A.; Reedijk, J., *Advanced Synthesis & Catalysis* **2004,** *346* (7), 805-811.

Ganem, B., *Journal of Organic Chemistry* **1975,** *40* (13), 1998-2000.

Gao, X. H.; Cui, Y. Y.; Levenson, R. M.; Chung, L. W. K.; Nie, S. M., *Nature Biotechnology* **2004,** *22* (8), 969-976.

Gao, X. H.; Yang, L. L.; Petros, J. A.; Marshal, F. F.; Simons, J. W.; Nie, S. M., *Current Opinion in Biotechnology* **2005,** *16* (1), 63-72.

Gaponik, N., *Journal of Materials Chemistry* **2010,** *20* (25), 5174-5181.

Gaponik, N.; Rogach, A. L., *Physical Chemistry Chemical Physics* **2010,** *12* (31), 8685-8693.

Garamszegi, L.; Donzel, C.; Carrot, G.; Nguyen, T. Q.; Hilborn, J., *Reactive & Functional Polymers* **2003,** *55* (2), 179-183.

Geneste, F.; Moinet, C.; Ababou-Girard, S.; Solal, F., *New Journal of Chemistry* **2005,** *29* (12), 1520-1526.

Genrich, F.; Schaumann, E., *Tetrahedron Letters* **2009,** *50* (45), 6187-6190.

Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K., *Macromolecules* **1993,** *26* (11), 2987-2988.

Gerion, D.; Pinaud, F.; Williams, S. C.; Parak, W. J.; Zanchet, D.; Weiss, S.; Alivisatos, A. P., *Journal of Physical Chemistry B* **2001,** *105* (37), 8861-8871.

Gerlock, J. L.; Zacmanidis, P. J.; Bauer, D. R.; Simpson, D. J.; Blough, N. V.; Salmeen, I. T., *Free Radical Research Communications* **1990,** *10* (1-2), 119-121.

Gheorghe, A.; Chinnusamy, T.; Cuevas-Yanez, E.; Hilgers, P.; Reiser, O., *Organic Letters* **2008,** *10* (19), 4171-4174.

Gheorghe, A.; Cuevas-Yanez, E.; Horn, J.; Bannwarth, W.; Narsaiah, B.; Reiser, O., *Synlett* **2006**, 2767-2770.

Gheorghe, A.; Matsuno, A.; Reiser, O., *Advanced Synthesis & Catalysis* **2006,** *348* (9), 1016-1020.

Giacobbe, E. M.; Mi, Q. X.; Colvin, M. T.; Cohen, B.; Ramanan, C.; Scott, A. M.; Yeganeh, S.; Marks, T. J.; Ratner, M. A.; Wasielewski, M. R., *Journal of the American Chemical Society* **2009,** *131* (10), 3700-3712.

Giepmans, B. N. G.; Adams, S. R.; Ellisman, M. H.; Tsien, R. Y., *Science* **2006,** *312* (5771), 217-224.

Giethlen, B.; Schaus, J. M., *Tetrahedron Letters* **1997,** *38* (49), 8483-8486.

Gijzeman, O. L.; Kaufman, F.; Porter, G., *Journal of the Chemical Society-Faraday Transactions I* **1973,** *69* (5), 727-737.

Gilhespy, M.; Lok, M.; Baucherel, X., *Catalysis Today* **2006,** *117* (1-3), 114-119.

Gilhespy, M.; Lok, M.; Baucherel, X., *Chemical Communications* **2005,** (8), 1085-1086.

Gill, R.; Zayats, M.; Willner, I., *Angewandte Chemie-International Edition* **2008,** *47* (40), 7602-7625.

Golubev, V. A.; Borislavskii, V. N.; Aleksandrov, A. L., *Bulletin of the Academy of Sciences of the Ussr Division of Chemical Science* **1977,** *26* (9), 1874-1881.

Gomez-Bujedo, S.; Fleury, E.; Vignon, M. R., *Biomacromolecules* **2004,** *5* (2), 565-571.

Gomtsyan, A., *Organic Letters* **2000,** *2* (1), 11-13.

Goto, A.; Scaiano, J. C.; Maretti, L., *Photochemical & Photobiological Sciences* **2007,** *6* (8), 833-835.

Graetz, B.; Rychnovsky, S.; Leu, W. H.; Farmer, P.; Lin, R., *Tetrahedron-Asymmetry* **2005,** *16* (21), 3584-3598.

Green, J. A.; Singer, L. A., *Journal of the American Chemical Society* **1974,** *96* (9), 2730-2733.

Green, J. A.; Singer, L. A.; Parks, J. H., *Journal of Chemical Physics* **1973,** *58* (7), 2690-2695.

Green, S. A.; Simpson, D. J.; Zhou, G.; Ho, P. S.; Blough, N. V., *Journal of the American Chemical Society* **1990,** *112* (20), 7337-7346.

Greenham, N. C.; Peng, X. G.; Alivisatos, A. P., *Physical Review B* **1996,** *54* (24), 17628-17637.

Grimaldi, S.; Finet, J. P.; Le Moigne, F.; Zeghdaoui, A.; Tordo, P.; Benoit, D.; Fontanille, M.; Gnanou, Y., *Macromolecules* **2000,** *33* (4), 1141-1147.

Grubbs, R. B., *Polymer Reviews* **2007,** *47* (2), 197-215.

Guillaneuf, Y.; Bertin, D.; Gigmes, D.; Versace, D. L.; Lalevee, J.; Fouassier, J. P., *Macromolecules* **2010,** *43* (5), 2204-2212.

Habibi, Y.; Vignon, M. R., *Cellulose* **2008,** *15* (1), 177-185.

Hafner, A.; Hrast, M.; Pecar, S.; Mravljak, J., *Tetrahedron Letters* **2009,** *50* (5), 564-566.

Haire, D. L.; Hilborn, J. W.; Janzen, E. G., *Journal of Organic Chemistry* **1986,** *51* (22), 4298-4300.

Hampton, P. D.; Whealon, M. D.; Roberts, L. M.; Yaeger, A. A.; Boydson, R., *Organic Process Research & Development* **2008,** *12* (5), 946-949.

Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J. H.; Abrams, J. N.; Forsyth, C. J., *Tetrahedron Letters* **2003,** *44* (1), 57-59.

Hartung, J., *Synlett* **1996,** (12), 1206-1208.

Hartung, J.; Schwarz, M., *Synlett* **1997,** (7), 848-850.

Hawker, C. J.; Bosman, A. W.; Harth, E., *Chemical Reviews* **2001,** *101* (12), 3661-3688.

Hay, B. P.; Beckwith, A. L. J., *Journal of Organic Chemistry* **1989,** *54* (18), 4330-4334.

Hayashi, M.; Sasano, Y.; Nagasawa, S.; Shibuya, M.; Iwabuchi, Y., *Chemical & Pharmaceutical Bulletin* **2011,** *59* (12), 1570-1573.

He, X. J.; Shen, Z. L.; Mo, W. M.; Sun, N.; Hu, B. X.; Hu, X. Q., *Advanced Synthesis & Catalysis* **2009,** *351* (1-2), 89-92.

Heafey, E.; Laferriere, M.; Scaiano, J. C., *Photochemical & Photobiological Sciences* **2007,** *6* (5), 580-584.

Herbelin, S. E.; Blough, N. V., *Journal of Physical Chemistry B* **1998,** *102* (42), 8170-8176.

Herbert, M.; Montilla, F.; Galindo, A., *Dalton Transactions* **2010,** *39* (3), 900-907.

Hermans, I.; Vereecken, L.; Jacobs, P. A.; Peeters, J., *Chemical Communications* **2004,** (9), 1140-1141.

Hernandez, E.; Soderquist, J. A., *Organic Letters* **2005,** *7* (24), 5397-5400.

Herrerias, C. I.; Zhang, T. Y.; Li, C. J., *Tetrahedron Letters* **2006,** *47* (1), 13-17.

Hideg, E.; Kalai, T.; Kos, P. B.; Asada, K.; Hideg, K., *Photochemistry and Photobiology* **2006,** *82* (5), 1211-1218.

Hideg, K.; Kalai, T.; Sar, C. P., *Journal of Heterocyclic Chemistry* **2005,** *42* (3), 437-450.

Hilf, S.; Kilbinger, A. F. M., *Macromolecules* **2009,** *42* (12), 4127-4133.

Hill, N. L.; Jarvis, J. L.; Pettersson, F.; Braslau, R., *Reactive & Functional Polymers* **2008,** *68* (1), 361-368.

Hirai, N.; Sawatari, N.; Nakamura, N.; Sakaguchi, S.; Ishii, Y., *Journal of Organic Chemistry* **2003,** *68* (17), 6587-6590.

Holczknecht, O.; Cavazzini, M.; Quici, S.; Shepperson, I.; Pozzi, G., *Advanced Synthesis & Catalysis* **2005,** *347* (5), 677-688.

Holczknecht, O.; Pozzi, G.; Quici, S., *Qsar & Combinatorial Science* **2006,** *25* (8-9), 736-741.

Hong, W. P.; Lee, K. J., *Synthesis-Stuttgart* **2006,** (6), 963-968.

Hosokawa, K.; Chen, P.; Lavin, M. F.; Bottle, S. E., *Free Radical Biology and Medicine* **2004,** *37* (7), 946-952.

Hou, X. D.; Li, Q. B.; Jia, L.; Li, Y.; Zhu, Y. D.; Cao, A. M., *Macromolecular Bioscience* **2009,** *9* (6), 551-562.

Hrdlovič, P.; Chmela, S.; Danko, M., *Journal of Photochemistry and Photobiology A-Chemistry* **1998,** *112* (2-3), 197-203.

Hrdlovič, P.; Chmela, S.; Danko, M.; Sarakha, M.; Guyot, G., *Journal of Fluorescence* **2008,** *18* (2), 393-402.

Huang, B. H.; Tomalia, D. A., *Journal of Luminescence* **2005,** *111* (4), 215-223.

Huang, J. Y.; Li, S. J.; Wang, Y. G., *Tetrahedron Letters* **2006,** *47* (32), 5637-5640.

Huang, P. Q.; Zheng, X.; Deng, X. M., *Tetrahedron Letters* **2001,** *42* (51), 9039-9041.

Hunsen, M., *Synthesis-Stuttgart* **2005,** (15), 2487-2490.

Hustedt, E. J.; Beth, A. H., *Annual Review of Biophysics and Biomolecular Structure* **1999,** *28*, 129-153.

Huynh, W. U.; Dittmer, J. J.; Alivisatos, A. P., *Science* **2002,** *295* (5564), 2425-2427.

Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S., *Journal of Organic Chemistry* **1990,** *55* (2), 462-466.

Ishii, Y.; Sakaguchi, S., *Catalysis Surveys from Japan* **1999,** *3* (1), 27-35.

Ivan, M. G.; Scaiano, J. C., *Photochemistry and Photobiology* **2003,** *78* (4), 416-419.

Iwabuchi, Y., *Journal of Synthetic Organic Chemistry Japan* **2008,** *66* (11), 1076-1084.

Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y., *Tetrahedron Letters* **1995,** *36* (38), 6923-6926.

Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G., *Australian Journal of Chemistry* **1990,** *43* (12), 2045-2062.

Jaiswal, J. K.; Mattoussi, H.; Mauro, J. M.; Simon, S. M., *Nature Biotechnology* **2003,** *21* (1), 47-51.

Jana, N. R.; Erathodiyil, N.; Jiang, J.; Ying, J. Y., *Langmuir* **2010,** *26* (9), 6503-6507.

Janzen, E. G., *Accounts of Chemical Research* **1971,** *4* (1), 31-40.

Janzen, E. G.; Lopp, I. G., *Journal of Magnetic Resonance* **1972,** *7* (1), 107-110.

Janzen, E. G.; Zhang, Y. K.; Haire, D. L., *Journal of the American Chemical Society* **1994,** *116* (9), 3738-3743.

Jenkins, A. D.; Jones, R. G.; Moad, G., *Pure and Applied Chemistry* **2010,** *82* (2), 483-491.

Jia, M.; Tang, Y.; Lam, Y. F.; Green, S. A.; Blough, N. V., *Analytical Chemistry* **2009,** *81* (19), 8033-8040.

Jiang, N.; Ragauskas, A. J., *Organic Letters* **2005,** *7* (17), 3689-3692.

Jiang, N.; Ragauskas, A. J., *Tetrahedron Letters* **2005,** *46* (19), 3323-3326.

Jin, T.; Fujii, F.; Yamada, E.; Nodasaka, Y.; Kinjo, M., *Combinatorial Chemistry & High Throughput Screening* **2007,** *10* (6), 473-479.

Jin, W. J.; Fernandez-Arguelles, M. T.; Costa-Fernandez, J. M.; Pereiro, R.; Sanz-Medel, A., *Chemical Communications* **2005,** (7), 883-885.

Jockusch, S.; Dedola, G.; Lem, G.; Turro, N. J., *Journal of Physical Chemistry B* **1999,** *103* (43), 9126-9129.

Johnson, C. G.; Caron, S.; Blough, N. V., *Analytical Chemistry* **1996,** *68* (5), 867-872.

Johnston, K. W.; Pattantyus-Abraham, A. G.; Clifford, J. P.; Myrskog, S. H.; MacNeil, D. D.; Levina, L.; Sargent, E. H., *Applied Physics Letters* **2008,** *92* (15).

Johnston, L. J.; Tencer, M.; Scaiano, J. C., *Journal of Organic Chemistry* **1986,** *51* (14), 2806-2808.

Jones, M.; Nedeljkovic, J.; Ellingson, R. J.; Nozik, A. J.; Rumbles, G., *Journal of Physical Chemistry B* **2003,** *107* (41), 11346-11352.

Joseph, J.; Kalyanaraman, B.; Hyde, J. S., *Biochemical and Biophysical Research Communications* **1993,** *192* (2), 926-934.

Jun, S.; Jang, E. J.; Chung, Y. S., *Nanotechnology* **2006,** *17* (19), 4806-4810.

Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P., *Tetrahedron* **1998,** *54* (22), 6051-6064.

Kachel, K.; Asuncionpunzalan, E.; London, E., *Biochemistry* **1995,** *34* (47), 15475-15479.

Kaiser, R. D.; London, E., *Biochemistry* **1998,** *37* (22), 8180-8190.

Kaizer, J.; Csonka, R.; Speier, G., *Journal of Molecular Catalysis A-Chemical* **2002,** *180* (1-2), 91-96.

Kaizer, J.; Csonka, R.; Speier, G., *Reaction Kinetics and Catalysis Letters* **2002,** *75* (2), 367-374.

Kaizer, J.; Pap, J.; Speier, G., *Food Chemistry* **2005,** *93* (3), 425-430.

Kalai, T.; Balog, M.; Jeko, J.; Hubbell, W. L.; Hideg, K., *Synthesis-Stuttgart* **2002,** (16), 2365-2372.

Kalai, T.; Hideg, E.; Vass, I.; Hideg, K., *Free Radical Biology and Medicine* **1998,** *24* (4), 649-652.

Kalai, T.; Jeko, J.; Berente, Z.; Hideg, K., *Synthesis-Stuttgart* **2006,** (3), 439-446.

Kalyuzhny, G.; Murray, R. W., *Journal of Physical Chemistry B* **2005,** *109* (15), 7012-7021.

Kamber, B.; Hartmann, A.; Eisler, K.; Riniker, B.; Rink, H.; Sieber, P.; Rittel, W., *Helvetica Chimica Acta* **1980,** *63* (4), 899-915.

Karade, N. N.; Tiwari, G. B.; Huple, D. B., *Synlett* **2005,** (13), 2039-2042.

Karimi, B.; Biglari, A.; Clark, J. H.; Budarin, V., *Angewandte Chemie-International Edition* **2007,** *46*, 7210-7213.

Kashiwagi, Y.; Ikezoe, H.; Ono, T., *Synlett* **2006,** (1), 69-72.

Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T., *Heterocycles* **1999,** *51* (8), 1945-1948.

Kashiwagi, Y.; Kurashima, F.; Chiba, S.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemical Communications* **2003,** (1), 114-115.

Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Tetrahedron Letters* **1999,** *40* (35), 6469-6472.

Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemical Communications* **1999,** (19), 1983-1984.

Kashiwagi, Y.; Nishimura, T.; Anzai, J., *Electrochimica Acta* **2002,** *47* (8), 1317-1320.

Kashiwagi, Y.; Ohsawa, A.; Osa, T.; Ma, Z.; Bobbitt, J. M., *Chemistry Letters* **1991,** (4), 581-584.

Kashiwagi, Y.; Yanagisawa, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemical Communications* **1996,** (24), 2745-2746.

Kawai, M.; Onaka, M.; Izumi, Y., *Journal of the Chemical Society-Chemical Communications* **1987,** (15), 1203-1204.

Kawle, B.; Adinarayana, M., *Indian Journal of Chemistry Section a-Inorganic Bio-Inorganic Physical Theoretical & Analytical Chemistry* **1994,** *33* (2), 124-127.

Kawle, B.; Rao, M. T.; Adinarayana, M., *Indian Journal of Chemistry Section a-Inorganic Bio-Inorganic Physical Theoretical & Analytical Chemistry* **1994,** *33* (11), 1021-1023.

Kawle, B.; Rao, M. T.; Adinarayana, M., *Indian Journal of Chemistry Section a-Inorganic Bio-Inorganic Physical Theoretical & Analytical Chemistry* **1996,** *35* (8), 667-670.

Keana, J. F. W.; Dinerste.Rj; Baitis, F., *Journal of Organic Chemistry* **1971,** *36* (1), 209-211.

Keddie, D. J.; Fairfull-Smith, K. E.; Bottle, S. E., *Organic & Biomolecular Chemistry* **2008,** *6* (17), 3135-3143.

Keddie, D. J.; Johnson, T. E.; Arnold, D. P.; Bottle, S. E., *Organic & Biomolecular Chemistry* **2005,** *3* (14), 2593-2598.

Kieber, D. J.; Blough, N. V., *Analytical Chemistry* **1990,** *62* (21), 2275-2283.

Kieber, D. J.; Blough, N. V., *Free Radical Research Communications* **1990,** *10* (1-2), 109-117.

Kim, B. J.; Bang, J.; Hawker, C. J.; Chiu, J. J.; Pine, D. J.; Jang, S. G.; Yang, S. M.; Kramer, E. J., *Langmuir* **2007,** *23* (25), 12693-12703.

Kim, S. S.; Jung, H. C., *Synthesis-Stuttgart* **2003,** (14), 2135-2137.

Kim, S. S.; Nehru, K., *Synlett* **2002,** (4), 616-618.

Kim, S.; Lee, I. Y.; Yoon, J. Y.; Oh, D. H., *Journal of the American Chemical Society* **1996,** *118* (21), 5138-5139.

Kim, S.; Lim, C. J.; Song, S. E.; Kang, H. Y., *Chemical Communications* **2001,** (15), 1410-1411.

Kim, S.; Lim, C. J.; Song, S. E.; Kang, H. Y., *Synlett* **2001,** (5), 688-690.

Kim, S.; Lim, Y. T.; Soltesz, E. G.; De Grand, A. M.; Lee, J.; Nakayama, A.; Parker, J. A.; Mihaljevic, T.; Laurence, R. G.; Dor, D. M.; Cohn, L. H.; Bawendi, M. G.; Frangioni, J. V., *Nature Biotechnology* **2004,** *22* (1), 93-97.

Kinugawa, M.; Masuda, Y.; Arai, H.; Nishikawa, H.; Ogasa, T.; Tomioka, S.; Kasai, M., *Synthesis-Stuttgart* **1996,** (5), 633-636.

Kitahara, Y.; Nakai, T.; Nakahara, S.; Akazawa, M.; Shimizu, M.; Kubo, A., *Chemical & Pharmaceutical Bulletin* **1991,** *39* (9), 2256-2263.

Klan, P.; Wirz, J., *Photochemistry of Organic Compounds: From Concepts to Practice*. John Wiley & Sons Ltd: West Sussex, 2009.

Klimov, V. I.; Mikhailovsky, A. A.; Xu, S.; Malko, A.; Hollingsworth, J. A.; Leatherdale, C. A.; Eisler, H. J.; Bawendi, M. G., *Science* **2000,** *290* (5490), 314-317.

Klimov, V., *Los Alamos Science* **2003,** *28*, 214-220.

Kloth, K.; Brunjes, M.; Kunst, E.; Joge, T.; Gallier, F.; Adibekian, A.; Kirschning, A., *Advanced Synthesis & Catalysis* **2005,** *347* (10), 1423-1434.

Knauer, B. R.; Napier, J. J., *Journal of the American Chemical Society* **1976,** *98* (15), 4395-4400.

Kollar, J.; Hrdlovič, P.; Chmela, S., *Journal of Photochemistry and Photobiology A-Chemistry* **2009,** *204* (2-3), 191-199.

Kollar, J.; Hrdlovič, P.; Chmela, S.; Sarakha, M.; Guyot, G., *Journal of Photochemistry and Photobiology A-Chemistry* **2005,** *170* (2), 151-159.

Kooser, R. G., *Macromolecules* **1987,** *20* (2), 435-436.

Kornblum, N.; Wade, P. A., *Journal of Organic Chemistry* **1973,** *38* (7), 1418-1420.

Kotake, Y.; Kuwata, K., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **1982,** *60* (12), 1610-1613.

Kraus, G. A.; Selvakumar, N., *Journal of Organic Chemistry* **1998,** *63* (26), 9846-9849.

Kraus, T.; Budesinsky, M.; Zavada, J., *Journal of Organic Chemistry* **2001,** *66* (13), 4595-4600.

Kuang, G. C.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Zhu, L., *Journal of Organic Chemistry* **2010,** *75* (19), 6540-6548.

Kubota, J.; Ido, T.; Kuroboshi, M.; Tanaka, H.; Uchida, T.; Shimamura, K., *Tetrahedron* **2006,** *62* (20), 4769-4773.

Kubota, J.; Shimizu, Y.; Mitsudo, K.; Tanaka, H., *Tetrahedron Letters* **2005,** *46* (52), 8975-8979.

Kumar, R. S.; Karthikeyan, K.; Perumal, P. T., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2008,** *86* (7), 720-725.

Kumpulainen, E. T. T.; Koskinen, A. M. P., *Chemistry-A European Journal* **2009,** *15* (41), 10901-10911.

Kuroboshi, M.; Goto, K.; Tanaka, H., *Synthesis-Stuttgart* **2009,** (6), 903-908.

Kuroboshi, M.; Yoshihisa, H.; Cortona, M. N.; Kawakami, Y.; Gao, Z.; Tanaka, H., *Tetrahedron Letters* **2000,** *41* (42), 8131-8135.

Kuzmin, V. A.; Tatikolov, A. S., *Chemical Physics Letters* **1977,** *51* (1), 45-47.

Laferriere, M.; Galian, R. E.; Maurel, V.; Scaiano, J. C., *Chemical Communications* **2006,** (3), 257-259.

Lai, G. F.; Anderson, W. K., *Synthetic Communications* **1997,** *27* (7), 1281-1283.

Lakowicz, J. R., *Principles of Fluorescence Spectroscopy*. 3rd ed.; Springer Science/Business Media: Singapore, 2006.

Landes, C. F.; Braun, M.; El-Sayed, M. A., *Journal of Physical Chemistry B* **2001,** *105* (43), 10554-10558.

Landes, C.; Burda, C.; Braun, M.; El-Sayed, M. A., *Journal of Physical Chemistry B* **2001,** *105* (15), 2981-2986.

Leanna, M. R.; Sowin, T. J.; Morton, H. E., *Tetrahedron Letters* **1992,** *33* (35), 5029-5032.

Lebedev, A. V.; Levitskaya, E. L.; Tikhonova, E. V.; Ivanova, M. V., *Biochemistry-Moscow* **2001,** *66* (8), 885-893.

Lee, C. U.; Roy, D.; Sumerlin, B. S.; Dadmun, M. D., *Polymer* **2010,** *51* (6), 1244-1251.

Lee, J.; Sundar, V. C.; Heine, J. R.; Bawendi, M. G.; Jensen, K. F., *Advanced Materials* **2000,** *12* (15), 1102-1105.

Lee, S.; Lee, B.; Kim, B. J.; Park, J.; Yoo, M.; Bae, W. K.; Char, K.; Hawker, C. J.; Bang, J.; Cho, J. H., *Journal of the American Chemical Society* **2009,** *131* (7), 2579-2587.

Lee, S.; Lim, C. J.; Kim, S., *Bulletin of the Korean Chemical Society* **2004,** *25* (11), 1611-1612.

Lei, M.; Hu, R. J.; Wang, Y. G., *Tetrahedron* **2006,** *62* (38), 8928-8932.

Lemoine, S.; Thomazeau, C.; Joannard, D.; Trombotto, S.; Descotes, G.; Bouchu, A.; Queneau, Y., *Carbohydrate Research* **2000,** *326* (3), 176-184.

Leyva, E.; Crispin, I.; Moctezuma, E.; Leyva, S., *Arkivoc* **2003**, 203-212.

Li, B. B.; Blough, N. V.; Gutierrez, P. L., *Free Radical Biology and Medicine* **2000,** *29* (6), 548-556.

Li, B. B.; Gutierrez, P. L.; Amstad, P.; Blough, N. V., *Chemical Research in Toxicology* **1999,** *12* (11), 1042-1049.

Li, B. B.; Gutierrez, P. L.; Blough, N. V., *Analytical Chemistry* **1997,** *69* (21), 4295-4302.

Li, J.; Wang, H. M.; Ma, H. M.; Zhang, D. Q.; Xiong, S. X., *Chinese Chemical Letters* **2005,** *16* (8), 1125-1128.

Li, X. Q.; Zhang, C., *Synthesis-Stuttgart* **2009,** (7), 1163-1169.

Liang, G. X.; Xu, Y.; Seiple, I. B.; Trauner, D., *Journal of the American Chemical Society* **2006,** *128* (34), 11022-11023.

Liang, J. G.; Huang, S.; Zeng, D. Y.; He, Z. K.; Ji, X. H.; Ai, X. P.; Yang, H. X., *Talanta* **2006,** *69* (1), 126-130.

Lidke, D. S.; Nagy, P.; Heintzmann, R.; Arndt-Jovin, D. J.; Post, J. N.; Grecco, H. E.; Jares-Erijman, E. A.; Jovin, T. M., *Nature Biotechnology* **2004,** *22* (2), 198-203.

Likhtenshtein, G. I., *Journal of Biochemical and Biophysical Methods* **1999,** *38* (1), 29-42.

Likhtenshtein, G. I., *Pure and Applied Chemistry* **2008,** *80* (10), 2125-2139.

Likhtenstein, G. I.; Ishii, K.; Nakatsuji, S., *Photochemistry and Photobiology* **2007,** *83* (4), 871-881.

Lilie, E. The Development of Fluorescent Nitroxide Probing Systems: Synthetic Progress Toward a Profluorescent Nitroxide Probe for Urushiol and Examination of Binding and Quenching in Nitroxide–CdSe Quantum Dot Complexes. Thesis (B.Sc.), University of California, Santa Cruz, 2009.

Lindner, J. P.; Roben, C.; Studer, A.; Stasiak, M.; Ronge, R.; Greiner, A.; Wendorff, H. J., *Angewandte Chemie-International Edition* **2009,** *48* (47), 8874-8877.

Liu, H. J.; Feng, W.; Kee, C. W.; Zhao, Y. J.; Leow, D.; Pan, Y. H.; Tan, C. H., *Green Chemistry* **2010,** *12* (6), 953-956.

Liu, H. T.; Owen, J. S.; Alivisatos, A. P., *Journal of the American Chemical Society* **2007,** *129* (2), 305-312.

Liu, H.; Dong, A.; Gao, C.; Tan, C.; Liu, H.; Zu, X.; Jiang, Y., *Bioorganic & Medicinal Chemistry* **2008,** *16* (23), 10013-10021.

Liu, I. S.; Lo, H. H.; Chien, C. T.; Lin, Y. Y.; Chen, C. W.; Chen, Y. F.; Su, W. F.; Liou, S. C., *Journal of Materials Chemistry* **2008,** *18* (6), 675-682.

Liu, J. T.; Jang, Y. J.; Shih, Y. K.; Hu, S. R.; Chu, C. M.; Yao, C. F., *Journal of Organic Chemistry* **2001,** *66* (18), 6021-6028.

Liu, L.; Guo, X. H.; Li, Y.; Zhong, X. H., *Inorganic Chemistry* **2010,** *49* (8), 3768-3775.

Liu, R. H.; Dong, C. Y.; Liang, X. M.; Wang, X. J.; Hu, X. Q., *Journal of Organic Chemistry* **2005,** *70* (2), 729-731.

Liu, R. H.; Liang, X. M.; Dong, C. Y.; Hu, X. Q., *Journal of the American Chemical Society* **2004,** *126* (13), 4112-4113.

Liu, W.; Howarth, M.; Greytak, A. B.; Zheng, Y.; Nocera, D. G.; Ting, A. Y.; Bawendi, M. G., *Journal of the American Chemical Society* **2008,** *130* (4), 1274-1284.

Liu, Z. Q.; Shang, X. J.; Chai, L. Z.; Sheng, Q. J., *Catalysis Letters* **2008,** *123* (3-4), 317-320.

Loh, T. P.; Li, X. R., *Tetrahedron* **1999,** *55* (35), 10789-10802.

Lozinsky, E. M.; Martina, L. V.; Shames, A. I.; Uzlaner, N.; Masarwa, A.; Likhtenshtein, G. I.; Meyerstein, D.; Martin, V. V.; Priel, Z., *Analytical Biochemistry* **2004,** *326* (2), 139-145.

Lozinsky, E.; Martin, V. V.; Berezina, T. A.; Shames, A. I.; Weis, A. L.; Likhtenshtein, G. I., *Journal of Biochemical and Biophysical Methods* **1999,** *38* (1), 29-42.

Lozinsky, E.; Novoselsky, A.; Shames, A. I.; Saphier, O.; Likhtenshtein, G. I.; Meyerstein, D., *Biochimica Et Biophysica Acta-General Subjects* **2001,** *1526* (1), 53-60.

Lu, N.; Lin, Y. C., *Tetrahedron Letters* **2007,** *48* (50), 8823-8828.

Luo, J. T.; Pardin, C.; Lubell, W. D.; Zhu, X. X., *Chemical Communications* **2007,** (21), 2136-2138.

Ma, M.; Zhang, X.; Peng, L. L.; Wang, J. B., *Tetrahedron Letters* **2007,** *48* (7), 1095-1097.

Ma, Q.; Cui, H.; Su, X., *Biosensors & Bioelectronics* **2009,** *25* (4), 839-844.

Ma, Y.; Yang, C.; Li, N.; Yang, X. R., *Talanta* **2005,** *67* (5), 979-983.

Ma, Z. K.; Huang, Q. T.; Bobbitt, J. M., *Journal of Organic Chemistry* **1993,** *58* (18), 4837-4843.

Ma, Z.; Bobbitt, J. M., *Journal of Organic Chemistry* **1991,** *56* (21), 6110-6114.

Majumder, M.; Karan, S.; Mallik, B., *Journal of Luminescence* **2011,** *131* (12), 2792-2802.

Maki, T.; Soh, N.; Fukaminato, T.; Nakajima, H.; Nakano, K.; Imato, T., *Analytica Chimica Acta* **2009,** *639* (1-2), 78-82.

Malenovska, M.; Martinez, S.; Neouze, M. A.; Schubert, U., *European Journal of Inorganic Chemistry* **2007,** (18), 2609-2611.

Manda, S.; Nakanishi, I.; Ohkubo, K.; Kawashima, T.; Matsumoto, K.; Ozawa, T.; Fukuzumi, S.; Ikota, N.; Anzai, K., *Chemistry Letters* **2007,** *36* (7), 914-915.

Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S.; Danishefsky, S. J., *Journal of Organic Chemistry* **2005,** *70* (26), 10619-10637.

Mannam, S.; Alamsetti, S. K.; Sekar, G., *Advanced Synthesis & Catalysis* **2007,** *349*, 2253-2258.

Mannam, S.; Sekar, G., *Tetrahedron-Asymmetry* **2009,** *20* (4), 497-502.

Marque, S.; Fischer, H.; Baier, E.; Studer, A., *Journal of Organic Chemistry* **2001,** *66* (4), 1146-1156.

Marshall, J. H., *Journal of Chemical Physics* **1971,** *54* (6), 2762-2763.

Martin, R., *Electronic Structure: Basic Theory and Practical Methods*. Cambridge University Press: UK, 2004.

Mason, B. P.; Bogdan, A. R.; Goswami, A.; McQuade, D. T., *Organic Letters* **2007,** *9*, 3449-3451.

Matko, J.; Ohki, K.; Edidin, M., *Biochemistry* **1992,** *31* (3), 703-711.

Matsumoto, N.; Iinuma, H.; Sawa, T.; Takeuchi, T., *Bioorganic & Medicinal Chemistry Letters* **1998,** *8* (21), 2945-2948.

Matsushita, M. M.; Izuoka, A.; Sugawara, T.; Kobayashi, T.; Wada, N.; Takeda, N.; Ishikawa, M., *Journal of the American Chemical Society* **1997,** *119* (19), 4369-4379.

Maurel, V.; Laferriere, M.; Billone, P.; Godin, R.; Scaiano, J. C., *Journal of Physical Chemistry B* **2006,** *110* (33), 16353-16358.

Mazitschek, R.; Mulbaier, M.; Giannis, A., *Angewandte Chemie-International Edition* **2002,** *41* (21), 4059-4061.

Medintz, I. L.; Uyeda, H. T.; Goldman, E. R.; Mattoussi, H., *Nature Materials* **2005,** *4* (6), 435-446.

Medvedeva, N.; Martin, V. V.; Weis, A. L.; Likhtenshten, G. I., *Journal of Photochemistry and Photobiology A-Chemistry* **2004,** *163* (1-2), 45-51.

Mei, Z. W.; Ma, L. J.; Kawafuchi, H.; Okihara, T.; Inokuchi, T., *Bulletin of the Chemical Society of Japan* **2009,** *82* (8), 1000-1002.

Mei, Z. W.; Omote, T.; Mansour, M.; Kawafuchi, H.; Takaguchi, Y.; Jutand, A.; Tsuboi, S.; Inokuchi, T., *Tetrahedron* **2008,** *64* (47), 10761-10766.

Meineke, P.; Rauen, U.; de Groot, H.; Korth, H. G.; Sustmann, R., *Chemistry-A European Journal* **1999,** *5* (6), 1738-1747.

Merbouh, N.; Bobbitt, J. M.; Bruckner, C., *Journal of Organic Chemistry* **2004,** *69* (15), 5116-5119.

Merbouh, N.; Bobbitt, J. M.; Bruckner, C., *Organic Preparations and Procedures International* **2004,** *36* (1), 1-31.

Merbouh, N.; Bobbitt, J. M.; Bruckner, C., *Tetrahedron Letters* **2001,** *42* (50), 8793-8796.

Merz, A.; Bachmann, H., *Journal of the American Chemical Society* **1995,** *117* (3), 901-908.

Meyers, A. I.; Temple, D. L.; Haidukew.D; Mihelich, E. D., *Journal of Organic Chemistry* **1974,** *39* (18), 2787-2793.

Miao, C. X.; He, L. N.; Wang, J. Q.; Gao, J., *Synlett* **2009,** (20), 3291-3294.

Miao, C. X.; He, L. N.; Wang, J. Q.; Wang, J. L., *Advanced Synthesis & Catalysis* **2009,** *351* (13), 2209-2216.

Micallef, A. S.; Blinco, J. P.; George, G. A.; Reid, D. A.; Rizzardo, E.; Thang, S. H.; Bottle, S. E., *Polymer Degradation and Stability* **2005,** *89* (3), 427-435.

Michaud, A.; Gingras, G.; Morin, M.; Beland, F.; Ciriminna, R.; Avnir, D.; Pagliaro, M., *Organic Process Research & Development* **2007,** *11* (4), 766-768.

Michel, C.; Belanzoni, P.; Gamez, P.; Reedijk, J.; Baerends, E. J., *Inorganic Chemistry* **2009,** *48* (24), 11909-11920.

Michon, P.; Rassat, A., *Journal of Organic Chemistry* **1974,** *39* (14), 2121-2124.

Miljevic, B.; Fairfull-Smith, K. E.; Bottle, S. E.; Ristovski, Z. D., *Atmospheric Environment* **2010,** *44* (18), 2224-2230.

Miljevic, B.; Heringa, M. F.; Keller, A.; Meyer, N. K.; Good, J.; Lauber, A.; Decarlo, P. F.; Fairfull-Smith, K. E.; Nussbaumer, T.; Burtscher, H.; Prevot, A. S. H.; Baltensperger, U.; Bottle, S. E.; Ristovski, Z. D., *Environmental Science & Technology* **2010,** *44* (17), 6601-6607.

Milkereit, G.; Morr, M.; Thiem, J.; Vill, V., *Chemistry and Physics of Lipids* **2004,** *127* (1), 47-63.

Miller, R. A.; Hoerrner, R. S., *Organic Letters* **2003,** *5* (3), 285-287.

Miller, R. C.; Bradley, J. S.; Hamilton, L. A., *Journal of the American Chemical Society* **1956,** *78* (20), 5299-5303.

Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F., *Chemical Communications* **2002,** (7), 688-689.

Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F., *European Journal of Organic Chemistry* **2004,** (1), 109-119.

Minisci, F.; Recupero, F.; Pedulli, G. F.; Lucarini, M., *Journal of Molecular Catalysis A-Chemical* **2003,** *204*, 63-90.

Minisci, F.; Recupero, F.; Rodino, M.; Sala, M.; Schneider, A., *Organic Process Research & Development* **2003,** *7* (6), 794-798.

Mitchell, G. P.; Mirkin, C. A.; Letsinger, R. L., *Journal of the American Chemical Society* **1999,** *121* (35), 8122-8123.

Mitsudo, K.; Kumagai, H.; Takabatake, F.; Kubota, J.; Tanaka, H., *Tetrahedron Letters* **2007,** *48* (51), 8994-8997.

Miyazawa, T.; Endo, T., *Tetrahedron Letters* **1986,** *27* (29), 3395-3398.

Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M., *Journal of Organic Chemistry* **1985,** *50* (8), 1332-1334.

Moad, G.; Rizzardo, E.; Solomon, D. H., *Macromolecules* **1982,** *15* (3), 909-914.

Moghaddam, L.; Blinco, J. P.; Colwell, J. M.; Halley, P. J.; Bottle, S. E.; Fredericks, P. M.; George, G. A., *Polymer Degradation and Stability* **2011,** *96* (4), 455-461.

Montanari, S.; Rountani, M.; Heux, L.; Vignon, M. R., *Macromolecules* **2005,** *38* (5), 1665-1671.

Morris, J. C.; McMurtrie, J. C.; Bottle, S. E.; Fairfull-Smith, K. E., *Journal of Organic Chemistry* **2011,** *76* (12), 4964-4972.

Morrow, B. J.; Keddie, D. J.; Gueven, N.; Lavin, M. F.; Bottle, S. E., *Free Radical Biology and Medicine* **2010,** *49* (1), 67-76.

Mu, J.; Gao, X. B.; Zhang, Y. Y.; Sun, H.; Liu, L. Y., *Journal of Dispersion Science and Technology* **2006,** *27* (1), 77-81.

Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J., *Journal of Organic Chemistry* **2005,** *70* (23), 9430-9435.

Mulder, W. J. M.; Koole, R.; Brandwijk, R. J.; Storm, G.; Chin, P. T. K.; Strijkers, G. J.; Donega, C. D.; Nicolay, K.; Griffioen, A. W., *Nano Letters* **2006,** *6* (1), 1-6.

Muratake, H.; Natsume, M.; Nakai, H., *Tetrahedron* **2004,** *60* (51), 11783-11803; Li, S. L.; Chiu, P., *Tetrahedron Letters* **2008,** *49* (11), 1741-1744.

Nagasawa, T.; Allakhverdiev, S. I.; Kimura, Y.; Nagata, T., *Photochemical & Photobiological Sciences* **2009,** *8* (2), 174-180.

Naik, N.; Braslau, R., *Tetrahedron* **1998,** *54* (5-6), 667-696.

Nakatsuji, S.; Anzai, H., *Journal of Materials Chemistry* **1997,** *7* (11), 2161-2174.

Nechab, M.; Kumar, D. N.; Philouze, C.; Einhorn, C.; Einhorn, J., *Angewandte Chemie-International Edition* **2007,** *46* (17), 3080-3083.

Nesvadba, P., *Chimia* **2006,** *60* (12), 832-840.

Neuman, D.; Ostrowski, A. D.; Mikhailovsky, A. A.; Absalonson, R. O.; Strouse, G. F.; Ford, P. C., *Journal of the American Chemical Society* **2008,** *130* (1), 168-175.

Newcomb, M.; Deeb, T. M.; Marquardt, D. J., *Tetrahedron* **1990,** *46* (7), 2317-2328.

Newcomb, M.; Dhanabalasingam, B., *Tetrahedron Letters* **1994,** *35* (29), 5193-5196.

Newcomb, M.; Kumar, M. U.; Boivin, J.; Crepon, E.; Zard, S. Z., *Tetrahedron Letters* **1991,** *32* (1), 45-48.

Nilsen, A.; Braslau, R., *Journal of Polymer Science Part A-Polymer Chemistry* **2006,** *44* (2), 697-717.

Noyori, R.; Aoki, M.; Sato, K., *Chemical Communications* **2003,** (16), 1977-1986.

Nyfeler, E.; Renaud, P., *Organic Letters* **2008,** *10* (5), 985-988.

Opeida, I. A.; Matvienko, A. G.; Ostrovskaya, O. Z., *Kinetics and Catalysis* **1995,** *36* (3), 441-441.

Osa, T.; Kashiwagi, Y.; Mukai, K.; Ohsawa, A.; Bobbitt, J. M., *Chemistry Letters* **1990,** (1), 75-78.

Pahari, P.; Rohr, J., *Journal of Organic Chemistry* **2009,** *74* (7), 2750-2754.

Palmer, A. M.; Chrismann, S.; Munch, G.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Senn-Bilfinger, J.; Feth, M. P.; Simon, W. A., *Bioorganic & Medicinal Chemistry* **2009,** *17* (1), 368-384.

Palmisano, G.; Ciriminna, R.; Pagliaro, M., *Advanced Synthesis & Catalysis* **2006,** *348* (15), 2033-2037.

Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Urchegui, R.; Linden, A., *Journal of Organic Chemistry* **1996,** *61* (13), 4400-4404.

Palomo, C.; Oiarbide, M.; Esnal, A.; Landa, A.; Miranda, J. I.; Linden, A., *Journal of Organic Chemistry* **1998,** *63* (17), 5838-5846.

Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A.; Linden, A., *Journal of Organic Chemistry* **2001,** *66* (12), 4180-4186.

Paola, F.; Marco, L.; Pamela, P.; Gian Franco, P., *ChemPhysChem* **2002,** *3* (9), 789-793.

Parker, K. A.; Su, D.-S., *Encyclopedia of Reagents for Organic Synthesis*. John Wiley: New York, 1995.

Perkins, M. J.; Berti, C.; Brooks, D. J.; Grierson, L.; Grimes, J. A. M.; Jenkins, T. C.; Smith, S. L., *Pure and Applied Chemistry* **1990,** *62* (2), 195-200.

Petzold, H.; Sadler, P. J., *Chemical Communications* **2008,** (37), 4413-4415.

Ponedel'kina, I. Y.; Khaibrakhmanova, E. A.; Odinokov, V. N., *Russian Chemical Reviews* **2010,** *79* (1), 63-75.

Pou, S.; Huang, Y. I.; Bhan, A.; Bhadti, V. S.; Hosmane, R. S.; Wu, S. Y.; Cao, G. L.; Rosen, G. M., *Analytical Biochemistry* **1993,** *212* (1), 85-90.

Poznyak, S. K.; Osipovich, N. P.; Shavel, A.; Talapin, D. V.; Gao, M. Y.; Eychmuller, A.; Gaponik, N., *Journal of Physical Chemistry B* **2005,** *109* (3), 1094-1100.

Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G., *Organic Letters* **2004,** *6* (3), 441-443.

Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F., *Journal of Organic Chemistry* **2009,** *74* (24), 9524-9527.

Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F., *Organic Letters* **2006,** *8*, 5485-5487.

Prakesch, M.; Gree, D.; Gree, R., *Tetrahedron* **2003,** *59* (44), 8833-8841.

Premachandran, R.; Banerjee, S.; John, V. T.; McPherson, G. L.; Akkara, J. A.; Kaplan, D. L., *Chemistry of Materials* **1997,** *9* (6), 1342-1347.

Qian, W. X.; Jin, E. L.; Bo, W. L.; Zhang, Y. M., *Tetrahedron* **2006,** *62* (4), 556-562.

Qu, J.; Katsumata, T.; Satoh, M.; Wada, J.; Igarashi, J.; Mizoguchi, K.; Masuda, T., *Chemistry-A European Journal* **2007,** *13* (28), 7965-7973.

Ragagnin, G.; Betzemeier, B.; Quici, S.; Knochel, P., *Tetrahedron* **2002,** *58* (20), 3985-3991.

Rahmat, D.; Sakloetsakun, D.; Shahnaz, G.; Perera, G.; Kaindl, R.; Bernkop-Schnurch, A., *International Journal of Pharmaceutics* **2011,** *411* (1-2), 10-17.

Rajadurai, C.; Enkelmann, V.; Zoppellaro, G.; Baumgarten, M., *Journal of Physical Chemistry B* **2007,** *111* (17), 4327-4334.

Raymo, F. M.; Yildiz, I., *Physical Chemistry Chemical Physics* **2007,** *9* (17), 2036-2043.

Reiss, P.; Bleuse, J.; Pron, A., *Nano Letters* **2002,** *2* (7), 781-784; Zaitseva, N.; Dai, Z. R.; Leon, F. R.; Krol, D., *Journal of the American Chemical Society* **2005,** *127* (29), 10221-10226.

Resch-Genger, U.; Grabolle, M.; Cavaliere-Jaricot, S.; Nitschke, R.; Nann, T., *Nature Methods* **2008,** *5* (9), 763-775.

Riahi, A.; Henin, F.; Muzart, J., *Tetrahedron Letters* **1999,** *40* (12), 2303-2306.

Rizzardo, E.; Solomon, D. H., *Polymer Bulletin* **1979,** *1* (8), 529-534.

Robbins, W. K.; Eastman, R. H., *Journal of the American Chemical Society* **1970,** *92* (20), 6077-6079.

Roben, C.; Studer, A.; Hemme, W. L.; Eckert, H., *Synlett* **2010,** (7), 1110-1114.

Roberti, T. W.; Cherepy, N. J.; Zhang, J. Z., *Journal of Chemical Physics* **1998,** *108* (5), 2143-2151.

Robinson, R. S.; Taylor, R. J. K., *Synlett* **2005,** (6), 1003-1005.

Rogach, A. L.; Franzl, T.; Klar, T. A.; Feldmann, J.; Gaponik, N.; Lesnyak, V.; Shavel, A.; Eychmuller, A.; Rakovich, Y. P.; Donegan, J. F., *Journal of Physical Chemistry C* **2007,** *111* (40), 14628-14637.

Rossetti, R.; Hull, R.; Gibson, J. M.; Brus, L. E., *Journal of Chemical Physics* **1985,** *82* (1), 552-559.

Roy, D.; Basu, P. K.; Raghunathan, P.; Eswaran, S. V., *Magnetic Resonance in Chemistry* **2003,** *41* (9), 671-678.

Rozantsev, E. G., *Free Nitroxyl Radicals*. Plenum Press: New York, 1970.

Ruggeri, S. G.; Bill, D. R.; Bourassa, D. E.; Castaldi, M. J.; Houck, T. L.; Ripin, D. H. B.; Wei, L. L.; Weston, N., *Organic Process Research & Development* **2003,** *7* (6), 1043-1047.

Rundlof, T.; Widmalm, G., *Analytical Biochemistry* **1996,** *243* (2), 228-233.

Russ, J. L.; Gu, J.; Tsai, K. H.; Glass, T.; Duchamp, J. C.; Dorn, H. C., *Journal of the American Chemical Society* **2007,** *129* (22), 7018-7027.

Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H., *Journal of Organic Chemistry* **1996,** *61* (4), 1194-1195.

Rychnovsky, S. D.; Vaidyanathan, R., *Journal of Organic Chemistry* **1999,** *64* (1), 310-312.

Rychnovsky, S. D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P. J., *Journal of Organic Chemistry* **1999,** *64* (18), 6745-6749.

Ryu, J. H.; Jeong, J. H., *Archives of Pharmacal Research* **1999,** *22* (6), 585-591.

Sakuratani, K.; Togo, H., *Synthesis-Stuttgart* **2003,** (1), 21-23.

Salmaso, S.; Caliceti, P.; Amendola, V.; Meneghetti, M.; Magnusson, J. P.; Pasparakis, G.; Alexander, C., *Journal of Materials Chemistry* **2009,** *19* (11), 1608-1615.

Sani-Souna-Sido, A.; Chassaing, S.; Pale, P.; Sommer, J., *Applied Catalysis A-General* **2008,** *336* (1-2), 101-108.

Saphier, O.; Silberstein, T.; Shames, A. I.; Likhtenshtein, G. I.; Maimon, E.; Mankuta, D.; Mazor, M.; Katz, M.; Meyerstein, D.; Meyerstein, N., *Free Radical Research* **2003,** *37* (3), 301-308.

Sar, C. P.; Jeko, J.; Fajer, P.; Hideg, K., *Synthesis-Stuttgart* **1999,** (6), 1039-1045.

Sarabia, F.; Sanchez-Ruiz, A., *Journal of Organic Chemistry* **2005,** *70* (23), 9514-9520.

Sathyamoorthy, R.; Sudhagar, P.; Kumar, R. S.; Sathyadevan, T. M., *Crystal Research and Technology* **2010,** *45* (1), 99-103.

Sato, S.; Suzuki, M.; Soma, T.; Tsunoda, M., *Spectrochimica Acta Part A-Molecular and Biomolecular Spectroscopy* **2008,** *70* (4), 799-804.

Sato, S.; Tsunoda, M.; Suzuki, M.; Kutsuna, M.; Takido-Uchi, K.; Shindo, M.; Mizuguchi, H.; Obara, H.; Ohya, H., *Spectrochimica Acta Part A-Molecular and Biomolecular Spectroscopy* **2009,** *71* (5), 2030-2039.

Sawatari, N.; Yokota, T.; Sakaguchi, S.; Ishii, Y., *Journal of Organic Chemistry* **2001,** *66* (23), 7889-7891.

Scaiano, J. C., *Tetrahedron* **1982,** *38* (6), 819-824.

Scaiano, J. C.; Laferriere, M.; Galian, R. E.; Maurel, V.; Billone, P., *Physica Status Solidi a-Applications and Materials Science* **2006,** *203* (6), 1337-1343.

Scaiano, J. C.; Paraskevopoulos, C. I., *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **1984,** *62* (11), 2351-2354.

Schamann, A.; Schafer, H. J., *Electrochimica Acta* **2005,** *50* (25-26), 4956-4972.

Schamann, M.; Schafer, H. J., *European Journal of Organic Chemistry* **2003,** (2), 351-358.

Schatz, A.; Grass, R. N.; Stark, W. J.; Reiser, O., *Chemistry-A European Journal* **2008,** *14* (27), 8262-8266.

Schlosser, M.; Brich, Z., *Helvetica Chimica Acta* **1978,** *61* (5), 1903-1911.

Schmidt, S. P.; Brooks, D. W., *Tetrahedron Letters* **1987,** *28* (7), 767-768.

Schnatbaum, K.; Schafer, H. J., *Synthesis-Stuttgart* **1999,** (5), 864-872.

Schoning, K. U., *Chimica Oggi-Chemistry Today* **2010,** *28* (1), 18-23.

Schroeder, T., *Nature* **2008,** *453* (7193), 345-351.

Selvan, S. T.; Patra, P. K.; Ang, C. Y.; Ying, J. Y., *Angewandte Chemie-International Edition* **2007,** *46* (14), 2448-2452.

Semmelhack, M. F.; Chou, C. S.; Cortes, D. A., *Journal of the American Chemical Society* **1983,** *105* (13), 4492-4494.

Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A., *Tetrahedron Letters* **1986,** *27* (10), 1119-1122.

Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S., *Journal of the American Chemical Society* **1984,** *106* (11), 3374-3376.

Sharma, S. N.; Pillai, Z. S.; Kamat, P. V., *Journal of Physical Chemistry B* **2003,** *107* (37), 10088-10093.

Sheldon, R. A.; Arends, I., *Advanced Synthesis & Catalysis* **2004,** *346* (9-10), 1051-1071.

Sheldon, R. A.; Arends, I., *Journal of Molecular Catalysis A-Chemical* **2006,** *251* (1-2), 200-214.

Sheldon, R. A.; Arends, I.; Ten Brink, G. J.; Dijksman, A., *Accounts of Chemical Research* **2002,** *35* (9), 774-781.

Shen, J.; Bottle, S.; Khan, N.; Grinberg, O.; Reid, D.; Micallef, A.; Swartz, H., *Applied Magnetic Resonance* **2002,** *22* (3), 357-368.

Shibamoto, A.; Sakaguchi, S.; Ishii, Y., *Organic Process Research & Development* **2000,** *4* (6), 505-508.

Shibuya, M.; Osada, Y.; Sasano, Y.; Tomizawa, M.; Iwabuchi, Y., *Journal of the American Chemical Society* **2011,** *133* (17), 6497-6500.

Shibuya, M.; Sasano, Y.; Tomizawa, M.; Hamada, T.; Kozawa, M.; Nagahama, N.; Iwabuchi, Y., *Synthesis-Stuttgart* **2011,** (21), 3418-3425.

Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y., *Chemical Communications* **2009,** (13), 1739-1741.

Shibuya, M.; Tomizawa, M.; Iwabuchi, Y., *Journal of Organic Chemistry* **2008,** *73* (12), 4750-4752.

Shibuya, M.; Tomizawa, M.; Iwabuchi, Y., *Organic Letters* **2008,** *10* (21), 4715-4718.

Shibuya, M.; Tomizawa, M.; Sasano, Y.; Iwabuchi, Y., *Journal of Organic Chemistry* **2009,** *74* (12), 4619-4622.

Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y., *Journal of the American Chemical Society* **2006,** *128* (26), 8412-8413.

Shimoyama, I.; Zhang, Y. T.; Wu, G. Z.; Negishi, E., *Tetrahedron Letters* **1990,** *31* (20), 2841-2844.

Siedlecka, R.; Skarzewski, J., *Synlett* **1996,** (8), 757-758.

Siedlecka, R.; Skarzewski, J., *Synthesis-Stuttgart* **1994,** (4), 401-404.

Siedlecka, R.; Skarzewski, J.; Mlochowski, J., *Tetrahedron Letters* **1990,** *31* (15), 2177-2180.

Sih, B. C.; Wolf, M., *Journal of Physical Chemistry C* **2007,** *111* (46), 17184-17192.

Sill, K.; Emrick, T., *Chemistry of Materials* **2004,** *16* (7), 1240-1243.

Singh, A. K.; Varma, R. S., *Tetrahedron Letters* **1992,** *33* (17), 2307-2310.

Singh, C.; Srivastav, N. C.; Puri, S. K., *Bioorganic & Medicinal Chemistry* **2004,** *12* (22), 5745-5752.

Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q., *Organic Letters* **2004,** *6* (24), 4603-4606.

Skaff, H.; Emrick, T., *Angewandte Chemie-International Edition* **2004,** *43* (40), 5383-5386.

Skaff, H.; Ilker, M. F.; Coughlin, E. B.; Emrick, T., *Journal of the American Chemical Society* **2002,** *124* (20), 5729-5733.

Skene, W. G.; Scaiano, J. C.; Listigovers, N. A.; Kazmaier, P. M.; Georges, M. K., *Macromolecules* **2000,** *33* (14), 5065-5072.

Smith, A. M.; Gao, X. H.; Nie, S. M., *Photochemistry and Photobiology* **2004,** *80* (3), 377-385.

Smith, A. M.; Nie, S., *Journal of the American Chemical Society* **2008,** *130* (34), 11278-11279.

Snee, P. T.; Somers, R. C.; Nair, G.; Zimmer, J. P.; Bawendi, M. G.; Nocera, D. G., *Journal of the American Chemical Society* **2006,** *128* (41), 13320-13321.

Sobhana, S. S. L.; Devi, M. V.; Sastry, T. P.; Mandal, A. B., *Journal of Nanoparticle Research* **2011,** *13* (4), 1747-1757.

Somers, R. C.; Bawendi, M. G.; Nocera, D. G., *Chemical Society Reviews* **2007,** *36* (4), 579-591.

Song, Z. G. J.; Zhao, M. Z.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E., *Journal of Organic Chemistry* **1999,** *64* (26), 9658-9667.

Sourkouni-Argirusi, G.; Kirschning, A., *Organic Letters* **2000,** *2* (24), 3781-3784.

Stork, G.; Franklin, P. J., *Australian Journal of Chemistry* **1992,** *45* (1), 275-284.

Stroh, C.; Mayor, M.; von Hanisch, C., *European Journal of Organic Chemistry* **2005,** (17), 3697-3703.

Stryer, L.; Griffith, O. H., *Proceedings of the National Academy of Sciences of the United States of America* **1965,** *54* (6), 1785-1791.

Subhani, M. A.; Beigi, M.; Eilbracht, P., *Advanced Synthesis & Catalysis* **2008,** *350* (18), 2903-2909.

Sudeep, P. K.; Emrick, T., *Polymer Reviews* **2007,** *47* (2), 155-163.

Surawski, N. C.; Miljevic, B.; Ayoko, G. A.; Roberts, B. A.; Elbagir, S.; Fairfull-Smith, K. E.; Bottle, S. E.; Ristovski, Z. D., *Environmental Science & Technology* **2011,** *45* (13), 5498-5505.

Surawski, N. C.; Miljevic, B.; Roberts, B. A.; Modini, R. L.; Situ, R.; Brown, R. J.; Bottle, S. E.; Ristovski, Z. D., *Environmental Science & Technology* **2010,** *44* (1), 229-235.

Suzuki, Y.; Katagi, T., *Journal of Agricultural and Food Chemistry* **2008,** *56* (22), 10811-10816.

Szwarc, M., *Nature* **1956,** *178* (4543), 1168-1169.

Takeda, T.; Watanabe, H.; Kitahara, T., *Synlett* **1997,** (10), 1149-1150.

Tanaka, M.; Fujita, R.; Nishide, H., *Polymer* **2007,** *48* (20), 5884-5888.

Tang, J. M.; Bhunia, S.; Sohel, S. M. A.; Lin, M. Y.; Liao, H. Y.; Datta, S.; Das, A.; Liu, R. S., *Journal of the American Chemical Society* **2007,** *129* (50), 15677-15683.

Tang, Y. L.; He, F.; Yu, M. H.; Wang, S.; Li, Y. L.; Zhu, D. B., *Chemistry of Materials* **2006,** *18* (16), 3605-3610.

Tanyeli, C.; Gumus, A., *Tetrahedron Letters* **2003,** *44* (8), 1639-1642.

Tao, L.; Geng, J.; Chen, G. J.; Xu, Y. J.; Ladmiral, V.; Mantovani, G.; Haddleton, D. M., *Chemical Communications* **2007,** (33), 3441-3443.

Tashino, Y.; Togo, H., *Synlett* **2004,** (11), 2010-2012.

Tatla, S.; Woodhead, V.; Foreman, J. C.; Chain, B. M., *Free Radical Biology and Medicine* **1999,** *26* (1-2), 14-24.

Tebben, L.; Studer, A., *Angewandte Chemie-International Edition* **2011,** *50* (22), 5034-5068.

Testa, M. L.; Ciriminna, R.; Hajji, C.; Garcia, E. Z.; Ciclosi, M.; Arques, J. S.; Pagliaro, M., *Advanced Synthesis & Catalysis* **2004,** *346* (6), 655-660.

Teuber, H. J.; Gross, H. J., *Chemische Berichte-Recueil* **1975,** *108* (6), 2097-2106.

Therkelsen, F. D.; Hansen, A. L. L.; Pedersen, E. B.; Nielsen, C., *Organic & Biomolecular Chemistry* **2003,** *1* (16), 2908-2918; Moorthy, J. N.; Samanta, S.; Koner, A. L.; Saha, S.; Nau, W. M., *Journal of the American Chemical Society* **2008,** *130* (41), 13608-13617.

Thomas-Smith, T. E.; Blough, N. V., *Environmental Science & Technology* **2001,** *35* (13), 2721-2726.

Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K., *Organic Letters* **2005,** *7* (14), 2933-2936.

Tkacheva, O. P.; Martin, V. V.; Volodarskii, L. B.; Buchachenko, A. L., *Bulletin of the Academy of Sciences of the Ussr Division of Chemical Science* **1981,** *30* (5), 913-915.

Tomasulo, M.; Yildiz, I.; Raymo, F. M., *Journal of Physical Chemistry B* **2006,** *110* (9), 3853-3855.

Tomizawa, M.; Shibuya, M.; Iwabuchi, Y., *Organic Letters* **2009,** *11* (8), 1829-1831.

Toribio, P. P.; Gimeno-Gargallo, A.; Capel-Sanchez, M. C.; de Frutos, M. P.; Campos-Martin, J. M.; Fierro, J. L. G., *Applied Catalysis A-General* **2009,** *363* (1-2), 32-39.

Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B., *Organic Letters* **2003,** *5* (7), 1031-1034.

Tromp, S. A.; Matijosyte, I.; Sheldon, R. A.; Arends, I.; Mul, G.; Kreutzer, M. T.; Moulijn, J. A.; de Vries, S., *Chemcatchem* **2010,** *2* (7), 827-833.

Turro, N. J., Modern Molecular Photochemistry. Benjamin Cummings Publishing Co.: Menlo Park, 1978; p 628.

Uber, J. S.; Vogels, Y.; van den Helder, D.; Mutikainen, I.; Turpeinen, U.; Fu, W. T.; Roubeau, O.; Gamez, P.; Reedijk, J., *European Journal of Inorganic Chemistry* **2007**, 4197-4206.

Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C., *Journal of the American Chemical Society* **2010,** *132* (29), 10012-10014.

Vatele, J. M., *Synlett* **2008,** (12), 1785-1788.

Vatele, J. M., *Synlett* **2009,** (13), 2143-2145.

Vatele, J. M., *Tetrahedron* **2010,** *66* (4), 904-912.

Vaughan, P. P.; Blough, N. V., *Environmental Science & Technology* **1998,** *32* (19), 2947-2953.

Veerman, E. C. I.; Nazmi, K.; van Hof, W.; Bolscher, J. G. M.; den Hertog, A. L.; Amerongen, A. V. N., *Biochemical Journal* **2004,** *381*, 447-452.

Veloso, D. P.; Rassat, A., *Journal of Chemical Research-S* **1979,** (5), 168-169.

Velusamy, S.; Kumar, A. V.; Saini, R.; Punniyamurthy, T., *Tetrahedron Letters* **2005,** *46* (22), 3819-3822.

Velusamy, S.; Srinivasan, A.; Punniyamurthy, T., *Tetrahedron Letters* **2006,** *47* (6), 923-926.

Versace, D. L.; Lalevee, J.; Fouassier, J. P.; Guillaneuf, Y.; Bertin, D.; Gigmes, D., *Macromolecular Rapid Communications* **2010,** *31* (15), 1383-1388.

Vogler, T.; Studer, A., *Synthesis-Stuttgart* **2008,** (13), 1979-1993.

Vollhardt, K. P. C.; Schore, N. E., *Organic Chemistry, Structure and Function* W. H. Freeman and Company: New York, 2003.

Volodarski, L. B.; Reznikov, V. A.; Ovcharenko, V. I., *Synthetic Chemistry of Stable Nitroxides*. CRC Press, Inc.: Boca Raton, Florida, 1994.

von Smoluchowski, M., *Zeitschrift Fur Physikalische Chemie-Stochiometrie Und Verwandtschaftslehre* **1917,** *92* (2), 129-168.

Wadhavane, P. D.; Angeles Izquierdo, M.; Galindo, F.; Isabel Burguete, M.; Luis, S. V., *Soft Matter* **2012,** *8* (16), 4373-4381.

Walker, G. W.; Sundar, V. C.; Rudzinski, C. M.; Wun, A. W.; Bawendi, M. G.; Nocera, D. G., *Applied Physics Letters* **2003,** *83* (17), 3555-3557.

Wang, H. M.; Zhang, D. Q.; Guo, X. F.; Zhu, L. Y.; Shuai, Z. G.; Zhu, D. B., *Chemical Communications* **2004,** (6), 670-671.

Wang, N. W.; Liu, R. H.; Chen, J. P.; Liang, X. M., *Chemical Communications* **2005**, 5322-5324.

Wang, X. L.; Liu, R. H.; Jin, Y.; Liang, X. M., *Chemistry-A European Journal* **2008,** *14* (9), 2679-2685.

Wang, Y. D.; DuBois, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P., *Science* **1998,** *279* (5350), 537-540.

Warren, N. J.; Muise, C.; Stephens, A.; Armes, S. P.; Lewis, A. L., *Langmuir* **2012,** *28* (5), 2928-2936.

Watanabe, S.; Nakahama, S.; Yamaguchi, K., *Makromolekulare Chemie-Macromolecular Chemistry and Physics* **1991,** *192* (8), 1891-1902.

Watkins, A. R., *Chemical Physics Letters* **1974,** *29* (4), 526-528.

Weik, S.; Nicholson, G.; Jung, G.; Rademann, J., *Angewandte Chemie-International Edition* **2001,** *40* (8), 1436-1439.

Weiss, D. S., *Journal of Photochemistry* **1977,** *6* (4), 301-304.

Wen, X. L.; Jia, Y. H.; Yang, L.; Liu, Z. L., *Talanta* **2001,** *53* (5), 1031-1036.

Wertz, S.; Studer, A., *Advanced Synthesis & Catalysis* **2011,** *353* (1), 69-72.

Whittaker, M. M.; Whittaker, J. W., *Biochemistry* **2001,** *40* (24), 7140-7148.

Williams, R. H.; Hamilton, L. A., *Journal of the American Chemical Society* **1952,** *74* (21), 5418-5420.

Winkle, M. R.; Ronald, R. C., *Journal of Organic Chemistry* **1982,** *47* (11), 2101-2108.

Wisher, A. C.; Bronstein, I.; Chechik, V., *Chemical Communications* **2006,** (15), 1637-1639.

Wu, X. E.; Ma, L.; Ding, M. X.; Gao, L. X., *Chemistry Letters* **2005,** *34* (3), 312-313.

Wu, X. E.; Ma, L.; Ding, M. X.; Gao, L. X., *Synlett* **2005,** (4), 607-610.

Wuister, S. F.; Donega, C. D.; Meijerink, A., *Journal of Physical Chemistry B* **2004,** *108* (45), 17393-17397.

Wuister, S. F.; Swart, I.; van Driel, F.; Hickey, S. G.; Donega, C. D., *Nano Letters* **2003,** *3* (4), 503-507.

Xie, Y.; Mo, W. M.; Xu, D.; Shen, Z. L.; Sun, N.; Hu, B. X.; Hu, X. Q., *Journal of Organic Chemistry* **2007,** *72* (11), 4288-4291.

Xu, H. P.; Xie, B. Y.; Yuan, W. Z.; Sun, J. Z.; Yang, F.; Dong, Y. Q.; Qin, A. J.; Zhang, S.; Wang, M.; Tang, B. Z., *Chemical Communications* **2007,** (13), 1322-1324.

Yadav, J. S.; Rajender, V.; Rao, Y. G., *Organic Letters* **2010,** *12* (2), 348-350.

Yamaguchi, K.; Kato, T.; Hirao, A.; Nakahama, S., *Makromolekulare Chemie-Rapid Communications* **1987,** *8* (4), 203-207.

Yamaguchi, M.; Miyazawa, T.; Takata, T.; Endo, T., *Pure and Applied Chemistry* **1990,** *62* (2), 217-222.

Yamakoshi, H.; Shibuya, M.; Tomizawa, M.; Osada, Y.; Kanoh, N.; Iwabuchi, Y., *Organic Letters* **2010,** *12* (5), 980-983.

Yan, Y.; Wang, S.; Liu, Z.; Wang, H.; Huang, D., *Analytical Chemistry* **2010,** *82* (23), 9775-9781.

Yanagisawa, Y.; Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J. M., *Chemistry Letters* **1996,** (12), 1043-1044.

Yang, G. Y.; Wang, W.; Zhu, W. M.; An, C. B.; Gao, X. Q.; Song, M. P., *Synlett* **2010,** (3), 437-440.

Yang, X. F.; Guo, X. Q., *Analyst* **2001,** *126* (10), 1800-1804.

Yang, X. F.; Guo, X. Q., *Analytica Chimica Acta* **2001,** *434* (2), 169-177.

Yao, S.; Schafer-Hales, K. J.; Cohanoschi, I.; Hernandez, F. E.; Belfield, K. D., *Synlett* **2006,** (12), 1863-1866.

Yasuda, K.; Ley, S. V., *Journal of the Chemical Society-Perkin Transactions 1* **2002,** (8), 1024-1025.

Yasuda, N.; Yamamoto, S.; Wada, Y.; Yanagida, S., *Journal of Polymer Science Part A-Polymer Chemistry* **2001,** *39* (24), 4196-4205.

Yildiz, I.; Deniz, E.; McCaughan, B.; Cruickshank, S. F.; Callan, J. F.; Raymo, F. M., *Langmuir* **2010,** *26* (13), 11503-11511.

Yildiz, I.; McCaughan, B.; Cruickshank, S. F.; Callan, J. F.; Raymo, F. M., *Langmuir* **2009,** *25* (12), 7090-7096.

Yin, W. L.; Chu, C. H.; Lu, Q. Q.; Tao, J. W.; Liang, X. M.; Liu, R. H., *Advanced Synthesis & Catalysis* **2010,** *352* (1), 113-118.

Yonekuta, Y.; Susuki, K.; Oyaizu, K. C.; Honda, K. J.; Nishide, H., *Journal of the American Chemical Society* **2007,** *129* (46), 14128-14129.

York, A. W.; Huang, F. Q.; McCormick, C. L., *Biomacromolecules* **2010,** *11* (2), 505-514.

Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y., *Journal of Organic Chemistry* **1997,** *62* (20), 6810-6813.

You, C. J.; Wilmes, S.; Beutel, O.; Lochte, S.; Podoplelowa, Y.; Roder, F.; Richter, C.; Seine, T.; Schaible, D.; Uze, G.; Clarke, S.; Pinaud, F.; Dahan, M.; Piehler, J., *Angewandte Chemie-International Edition* **2010,** *49* (24), 4108-4112.

Yu, W. W.; Qu, L. H.; Guo, W. Z.; Peng, X. G., *Chemistry of Materials* **2003,** *15* (14), 2854-2860.

Zakrzewski, J.; Grodner, J.; Bobbitt, J. M.; Karpinska, M., *Synthesis-Stuttgart* **2007**, 2491-2494.

Zanka, A., *Chemical & Pharmaceutical Bulletin* **2003,** *51* (7), 888-889.

Zard, S. Z., *Angewandte Chemie-International Edition in English* **1997,** *36* (7), 673-685.

Zelent, B.; Kusba, J.; Gryczynski, I.; Johnson, M. L.; Lakowicz, J. R., *Journal of Physical Chemistry* **1996,** *100* (47), 18592-18602.

Zhang, M. A.; Chen, C. C.; Ma, W. H.; Zhao, J. C., *Angewandte Chemie-International Edition* **2008,** *47* (50), 9730-9733.

Zhang, Q. L.; Russell, T. P.; Emrick, T., *Chemistry of Materials* **2007,** *19* (15), 3712-3716.

Zhao, M. Z.; Li, J.; Mano, E.; Song, Z. G.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J., *Journal of Organic Chemistry* **1999,** *64* (7), 2564-2566.

Zhao, X. F.; Zhang, C., *Synthesis-Stuttgart* **2007,** (4), 551-557.

Zhu, N.; Ling, J.; Zhu, Y. H.; Sun, W. L.; Shen, Z. Q., *Journal of Polymer Science Part A-Polymer Chemistry* **2010,** *48* (19), 4366-4369.

Ziessel, R.; Stroh, C., *Organic Letters* **2003,** *5* (14), 2397-2400.

Ziessel, R.; Stroh, C., *Synthesis-Stuttgart* **2003,** (14), 2145-2154.

Zimmer, H.; Lankin, D. C.; Horgan, S. W., *Chemical Reviews* **1971,** *71* (2), 229-246.

Zimmer, J. P.; Kim, S. W.; Ohnishi, S.; Tanaka, E.; Frangioni, J. V.; Bawendi, M. G., *Journal of the American Chemical Society* **2006,** *128* (8), 2526-2527.

Zotti, G.; Vercelli, B.; Berlin, A.; Chin, P. T. K.; Giovanella, U., *Chemistry of Materials* **2009,** *21* (11), 2258-2271.