Synthesis of Chiral Nitroxides and an Unusual Racemization Reaction

Scott D. Rychnovsky,* Thomas Beauchamp, Rajappa Vaidyanathan, and Tricia Kwan

Department of Chemistry, University of California, Irvine, California 92697-2025

Received May 8, 1998

Lai's protocol for the synthesis of nitroxides has been extended to the synthesis of several new chiral piperazine and morpholine nitroxides. This strategy utilizes the Bargellini reaction as the key bond-forming step. Several optically pure nitroxides incorporating α-aromatic and α-spiro centers were prepared by this route. These chiral nitroxides will be of interest as enantioselective oxidants, as traps for prochiral radicals, and in the preparation of new materials. One of these nitroxides, compound **43**, was found to racemize under mild oxidizing conditions. The mechanism for this unusual racemization reaction was investigated.

Introduction

The recent years have witnessed an increased activity in the area of chiral nitroxide synthesis. Nitroxides are persistent free radicals that exhibit remarkable stability primarily due to the absence of dimerization and disproportionation. Their unique properties have sparked considerable interest from theoretical, chemical, and biological standpoints.[1] Chiral nitroxides have been used as catalysts in the kinetic resolution of alcohols via enantioselective oxidation.[2] They have also been employed in stereoselective coupling reactions with prochiral radicals.[3] In addition, nitroxides have found widespread application in the development of paramagnetic chiral liquid crystals[4] and in the control of living free radical polymerization processes.[5] A recent review details the progress made in the area of chiral nitroxide radicals.[6] However, very few of the chiral nitroxides synthesized to date possess a stereogenic center adjacent to the NO radical moiety. We were particularly interested in synthesizing six-membered ring chiral nitroxide radicals bearing an aromatic substituent α to the nitroxyl center.[7] The major difficulty in preparing such nitroxides is in installing the two quaternary centers adjacent to the nitrogen. Traditionally these substituents are installed stepwise either via alkylation of nitroso compounds or by nucleophilic addition to nitrones. Both of these reactions are highly substrate dependent and are not amenable to the synthesis of structurally diverse nitroxides.[8]

We were attracted by Lai's protocol for the synthesis of hindered morpholinones and piperazinones (Figure 1).[9] This method involves the coupling of an amino alcohol **1** and a ketone **2** to produce compound **3** that contains the two quaternary centers adjacent to the amine in a single step. Further transformation of carboxylate **3** produces the morpholinone nitroxide **5** or morpholine nitroxide **6**. Lai prepared just a few hindered morpholines and morpholinones by this method,[9] but the general approach appears to be versatile and would allow a rapid entry into many different chiral nitroxides from a variety of amino alcohols **1** and ketones **2**. Our extension of the Lai protocol to chiral nitroxide synthesis is described below.

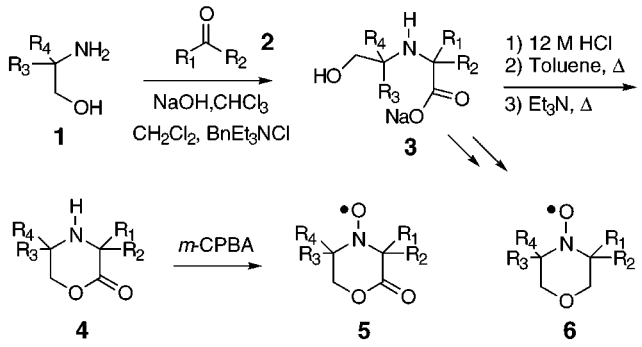


Figure 1. Lai's synthesis of morpholine and morpholinone nitroxides.

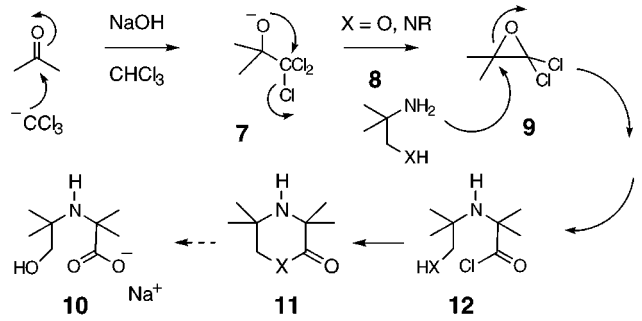


Figure 2. Proposed mechanism of the Bargellini reaction between acetone and 2-amino-2-methyl-1-propanol or 1,2-diaminopropanes.

The generally accepted mechanism for the initial coupling reaction is shown in Figure 2. This is an example of the Bargellini reaction in which a ketone, nucleophile, and chloroform react in the presence of a

(1) Volodarsky, L. B.; Reznikov, V. A.; Ovcharenko, V. I. *Synthetic Chemistry of Stable Nitroxides*; CRC Press: Boca Raton, FL, 1994.
(2) (a) Ma, Z.; Huang, Q.; Bobbitt, J. M. *J. Org. Chem.* **1993**, *58*, 4837−4843. (b) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194−1195.
(3) Braslau, R.; Burrill, L. C., II; Mahal, L. K.; Wedeking, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 237−238.
(4) Tamura, R.; Suzuki, S.; Azuma, N.; Matsumoto, A.; Toda, F.; Kamimura, A.; Hori, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 878−879.
(5) Puts, R. D.; Sogah, D. Y. *Macromolecules* **1996**, *29*, 3323−3325.
(6) Naik, N.; Braslau, R. *Tetrahedron* **1998**, *54*, 667−696.
(7) Although there are several good routes for the synthesis of five-membered ring nitroxides, very few methods exist for the synthesis of six-membered ring chiral nitroxides. See refs 6 and 8.
(8) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Durif, A.; Averbuch, M.-T.; Pierre, J.-L. *Tetrahedron Lett.* **1998**, *39*, 2565−2568.

S0022-3263(98)00883-4 CCC: $15.00
Published on Web 08/20/1998

Table 1. Cyclization of Diamine 16 with Ketones[a]

entry	ketone	time (h)	yield (%)
1	acetone	24	76
2	cyclohexanone	16	87
3	acetophenone	16	0
4	1-indanone	24	0
5	*p*-nitroacetophenone	48	16
6	butanone	16	27

[a] All reactions were carried out using 1.5 equiv of $CHCl_3$, 2 equiv of ketone, 5 equiv of NaOH (50%), catalytic NaCN, and $BnEt_3N^+Cl^-$ in CH_2Cl_2 at 10 °C.

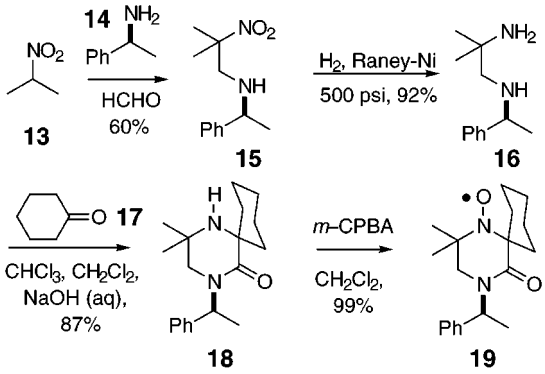
strong base.[10] Deprotonation of chloroform by sodium hydroxide followed by nucleophilic attack on the ketone yields dichloro epoxide **9**. The hindered N−C bond is formed via regioselective opening of **9** by the nucleophile, an amino alcohol[9] or diamine[9] in the present example. An amino alcohol (e.g. **8**, X = O) would close to the lactone **11** (X = O) via the acid choride **12**. Subsequent hydrolysis of the lactone in the strongly basic reaction medium leads to the observed product **10**. A diamine (e.g. **8**, X = NR), on the other hand, cyclizes to the stable piperazinone **11** (X = NR). Chiral morpholines, morpholinones, piperazines, and piperazinones should all be accessible on the basis of this unique reaction.

Results and Discussion

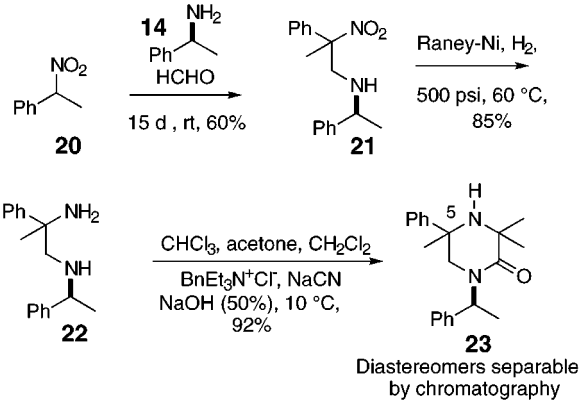
Synthesis of Piperazinone and Piperazine Nitroxides. Synthesis of chiral piperazine and piperazinone nitroxides was our initial objective. With the ultimate goal of producing optically pure nitroxides, (*S*)-1-phenethylamine (**14**) was introduced to facilitate the separation of diastereomers produced in the Bargellini reaction with unsymmetric ketones. Diamine **16** was prepared by condensation of 2-nitropropane with formaldehyde and **14** followed by hydrogenation in an extension of Senkus's procedure.[11] Bargellini reaction with cyclohexanone using Lai's conditions gave the expected piperazinone **18** in excellent yield. Oxidation with *m*-CPBA gave the stable nitroxide **19**. Nitroxide **19** was prepared in four steps and 48% overall yield from commercially available materials.

Nitroxide **19** is chiral by virtue of the phenethylamine center, but the stereogenic center is remote from the nitroxide center and is unlikely to exert any interesting effect on further chemistry. Introduction of a stereogenic center α to the hindered amine was the next obvious step, and this is where the limitations of the Bargellini coupling became apparent. Table 1 shows our attempts to couple several ketones with diamine **16**. Both acetone and cyclohexanone work well. Indanone spontaneously polymerized upon addition of base. Acetophenone gave essentially none of the desired product, and *p*-nitroacetophenone gave only 16% yield of the piperazinone. Reaction with butanone afforded the cyclized product in 27% yield. The sensitivity of the reaction to variations in the ketone structure precluded a general "combinatorial" synthesis of piperazinones, and so we shifted our focus to exploring structural variations in the diamine structure.

Scheme 1



Scheme 2



The diamine route was successful for the introduction of chiral centers adjacent to the hindered amine, Scheme 2. Condensation of α-nitroethylbenzene[12] **20** with formaldehyde and **14** gave the expected adduct **21** in good yield, as a mixture of diastereomers. Hydrogenation over Raney Ni furnished diamine **22** as a mixture of diastereomers which was used without separation. Coupling with acetone using Lai's conditions gave piperazinone **23** in excellent yield. The two diastereomers were easily separated by flash chromatography, producing piperazinone **23** with either configuration at the C5 center. The α-methylbenzylamine acts as an internal resolving agent and facilitates separation of the C-5 epimers of piperazinone **23**. Thus the chiral diamine route is effective for the preparation of piperazines with stereogenic centers adjacent to the hindered nitrogen.

This approach was also used to prepare optically pure chiral nitroxide **29**, Scheme 3. The 1-nitrotetralin (**24**) was prepared by oxidation of the corresponding oxime[13] or by displacement of the corresponding bromide with $NaNO_2$.[12] Condensation with formaldehyde and amine **14** followed by reduction proceeded uneventfully. Bargellini coupling with acetone under Lai's conditions gave piperazinone **26** in excellent yield as a 1.3:1 mixture of diastereomers. Unlike in the previous example, the diastereomeric piperazinones were not separable by flash chromatography. LAH reduction cleanly converted **26** to the corresponding piperazine **27**. The diastereomers of **27** were not separable by chromatography, but crystallization of the (+)-camphorsulfonic acid (CSA) salt was

(9) (a) Lai, J. T. *J. Org. Chem.* **1980**, *45*, 754−755. (b) Lai, J. T. *Synthesis* **1981**, 41−42. (c) Lai, J. T. *Synthesis* **1984**, 122−123. (d) Lai, J. T. *Synthesis* **1984**, 124−125.

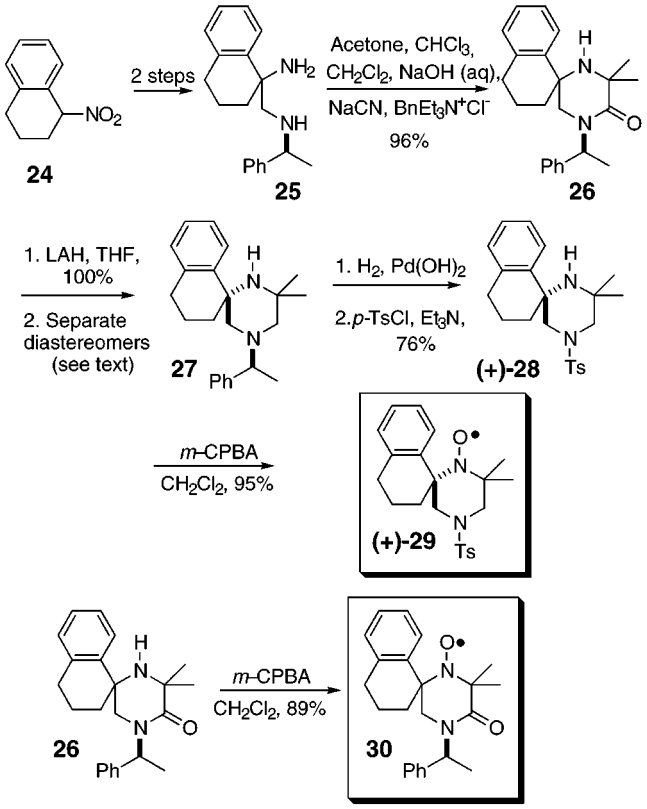
(10) (a) Link, G. German Patent 80,986 (July 14, 1894) from: *Chem. Zentr.* **1895**, *66* (II), 70. (b) Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 329−338.

(11) Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10−12.

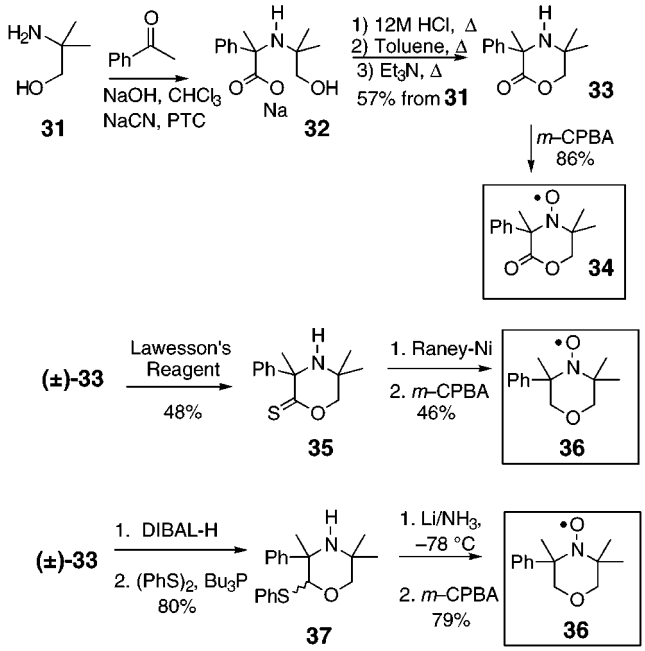
(12) Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38*, 1418−1420.

(13) Olah, G. A.; Ramaiah, P.; Lee, C.-S.; Prakash, G. K. S. *Synlett* **1992**, 337−339.

Scheme 3



Scheme 4



successful.[14] Hydrogenation of diastereomerically pure **27** over Pearlman's catalyst led to cleavage of the phenethyl group without significant cleavage at the tertiary benzylic amine bond. Tosylation followed by *m*-CPBA oxidation gave the optically pure nitroxide in good overall yield. The absolute configuration α to the nitroxyl center has not been determined. The enantiomeric excess of **29** should be >97% based on the diastereomeric excess of **27** as determined by ^{1}H NMR analysis.[15] Oxidation of the piperazinone **26** also led to the chiral nitroxide **30**. Thus, the chiral diamine route to optically active nitroxides is effective where the appropriate nitroalkanes are available or easily prepared.

Synthesis of Morpholine and Morpholinone Nitroxides. Chiral morpholine and morpholinone nitroxides should also be available using the Bargellini reaction. Scheme 4 outlines a route to these nitroxides from 2-methyl-2-amino-1-propanol (**31**). We were surprised to find that the Bargellini coupling with acetophenone worked very well in this case. The same reaction had been unsuccessful with the diamine **16**. The sodium salt **32** precipitated from the reaction and was isolated by filtration. Acidification followed by heating in toluene and neutralization with Et_3N gave the lactone **33** in 57% overall yield from the amino alcohol **31**. Oxidation with *m*-CPBA completed this simple and effective synthesis of morpholinone nitroxide **34**.

The racemic lactone **33** could be deoxygenated to morpholine nitroxide **36**. Lai had shown that simple morpholines could be prepared from the morpholinones by reduction to the diol followed by dehydration−cyclization using methanesulfonic acid. Preliminary attemps to prepare more complex morpholines by methanesulfonic acid-mediated dehydration were not promising, so two new routes were developed. Lactone **33** was converted to the thionolactone **35** by treatment with Lawesson's reagent. Subsequent reductive desulfurization and *m*-CPBA oxidation gave the morpholine nitroxide **36**, but the overall yield was disappointing. An alternative deoxygenation began with the DIBAL-H reduction of lactone **33** followed by conversion to the phenylthio acetal. Lithium−ammonia reduction removed the phenylthio acetal, and *m*-CPBA oxidation furnished the morpholine nitroxide **36** in a good overall yield.

Another target of interest was the indane morpholine nitroxide **43**. All attempts to directly couple indanone with commercially available amino alcohol **31** were unsuccessful and led only to polymerization of the indanone.[16] Synthesis of the racemic nitroxide followed our general approach to piperazine nitroxides, Schemes 2 and 3. The 1-nitroindane[17] was prepared by oxidation of the corresponding oxime with sodium perborate.[13] Base-promoted condensation with formaldehyde and hydrogenation of the nitro group gave amino alcohol **39** in good yield. Bargellini coupling with acetone gave the expected carboxylate salt, which was acidified and dehydrated with CSA in toluene. In cases such as this one with the aromatic ring remote from the carbonyl, acidification of the carboxylate salt with aqueous HCl only led to decomposition. Dehydration of the lactone **40** was carried out via the phenylthio acetal **41**. In this case acetylation of the lactol followed by TMSOTf-catalyzed introduction of the thiophenol was more effective than

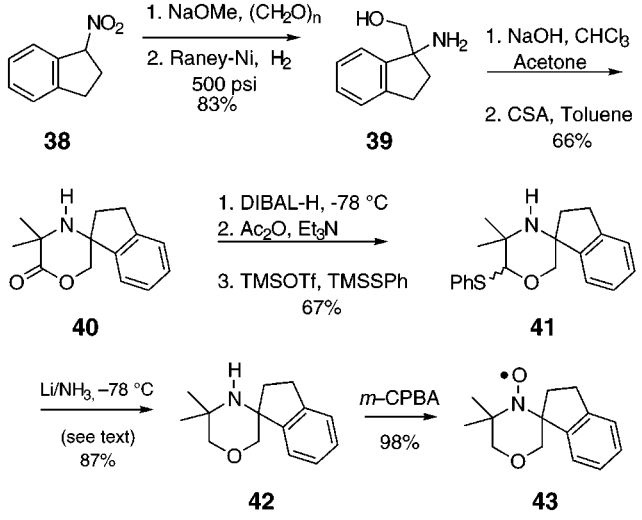
(14) The presence of the chiral phenethyl moiety allowed us to monitor the resolution by ^{1}H NMR analysis.

(15) When a 1: 3 mixture of diastereomers of **27** was carried through the sequence, the resulting nitroxide **29** had an $[\alpha]_D^{23}$ of −30.8 (c = 1.0, $CHCl_3$), which corresponds to an ee of ca. 50% based on the optical rotation of enantiomerically pure (+)-**29**.

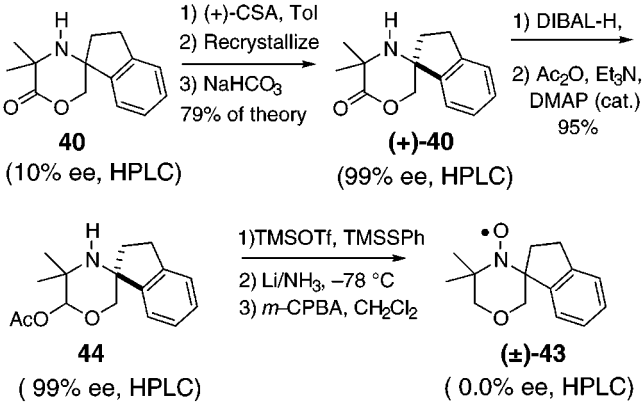
(16) The trichloromethyl adduct of indanone was prepared in an effort to avoid the use of base sensitive indanone and to bypass the first step of the mechanism (Figure 2, intermediate **7**), but on treatment with mild base it instantly reverted to the indanone, which promptly polymerized.

(17) The 1-nitroindane has also been prepared by oxidation of 1-aminoindane with CF_3COCH_3: (a) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887−3889. (b) Murray, R. W.; Singh, M.; Rath, N. *Tetrahedron: Asymmetry* **1996**, *7*, 1611−1619.

Scheme 5



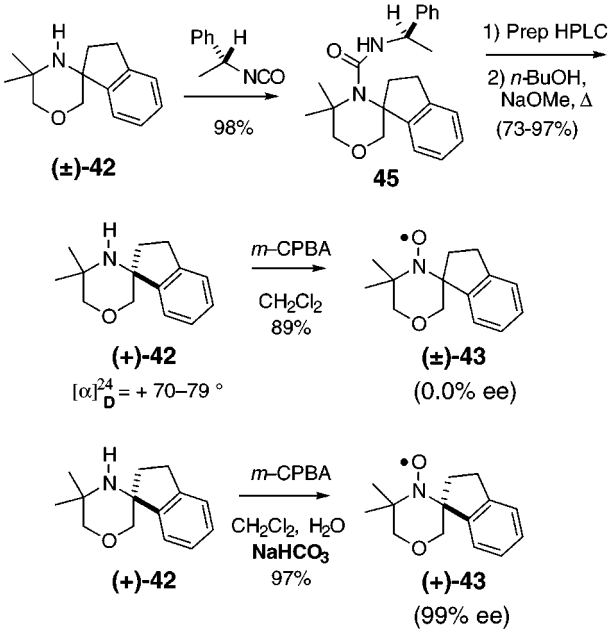
Scheme 6



$(PhS)_2-PBu_3$ treatment. Unlike the reduction of thioacetal **37**, Li/NH_3 reduction of **41** resulted in Birch reduction of the aromatic ring. Overreduction was circumvented by quenching the reaction with thioanisole. Oxidation with *m*-CPBA gave the racemic nitroxide **43** in good overall yield. The synthesis of **43** demonstrates that complex chiral morpholine nitroxides can be prepared from the corresponding nitro alkanes.

Preparation and Unexpected Racemization of a Chiral Nitroxide. We set out to prepare optically pure indane nitroxide **43** but were in for a surprise. Scheme 6 illustrates the initial attempt to synthesize optically pure **43**. Lactone **40** was synthesized in 10% ee starting from optically enriched amino alcohol **39** (10% ee).[18] Resolution using (+)-CSA led to the isolation of the major enantiomer in 79% of theory in 99% ee.[22] (+)-**40** was reduced with DIBAL-H and acetylated to give a diastereomeric mixture of lactol acetates. Comparison of the HPLC trace with that of the racemic material showed

Scheme 7



that both diastereomers of the acetate **44** were optically pure. The remainder of the deoxygenation and oxidation sequence proceeded uneventfully to give **43**. We were very surprised to find that **43** exibited a rotation of zero, and further analysis on a chiral HPLC column showed that it was racemic.[19]

The sequence from optically pure **44** to racemic **43** involved a Lewis acid promoted exchange, dissolving metal reduction, and oxidation. Both the Lewis acid and the reduction step might be responsible for a reversible cleavage of the tertiary benzylic amine. Resolution of morpholine **42** would circumvent racemization in these steps. Resolution via the CSA salt was unsuccessful, but treatment with (*R*)-(+)-(α)-methylbenzyl isocyanate gave the diastereomeric carbamates **45** in nearly quantitative yield, Scheme 7. The diastereomers were separated by preparative HPLC, and the carbamate was cleaved to give optically active morpholine **42**. The optical purity of **42** could not be directly assayed by HPLC, but it did come from a single diastereomer of **45** and exhibited a nonzero rotation. Once again, *m*-CPBA oxidation of **42** gave racemic nitroxide **43**.[19] These experiments demonstrated that the racemization was taking place in the *m*-CPBA oxidation rather than the previously suspected Lewis acid treatment or dissolving metal reduction.

Small amounts of **43** were resolved by preparative HPLC using a chiralpak-AD analytical column. Upon further experimentation we found that the optically pure morpholine could be oxidized to **43** without racemization using *m*-CPBA under buffered, biphasic conditions. The most expedient synthesis of optically pure **43** would appear to be resolution of the racemate on a chiral HPLC column or resolution of lactone **40** with (+)-CSA followed by deoxygenation and *buffered m*-CPBA oxidation.[20]

Mechanism of the Racemization of Indane Nitroxide 43. How does *unbuffered m*-CPBA lead to racemization in the preparation of nitroxide **43**? Nitroxide **43** itself does not racemize on standing for weeks at room temperature, either in solution or neat. Four mechanistic possiblities for the racemization are outlined in Figure 3. Mechanism A involves reversible opening and closing of the protonated amine **46**. In mechanism

(18) The enantiomeric excess of **40** was analyzed by chiral HPLC using a 10 × 250 mm chiralpak-AD column eluting with 4% *i*-PrOH/ hexanes at 0.5 mL/min; t_R = 17.3 min (major) and 18.8 min (minor).

(19) The enantiomeric excess of **43** was analyzed by chiral HPLC using a 10 × 250 mm chiralpak-AD column eluting with 2% *i*-PrOH/ hexanes at 0.5 mL/min; t_R = 17.1 and 18.6 min.

(20) We have not proved that the deoxygenation proceeds without racemization.

(21) Ciganek, E.; Read, J. M.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795–5802.

(22) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1975**, *40*, 3145–3147.

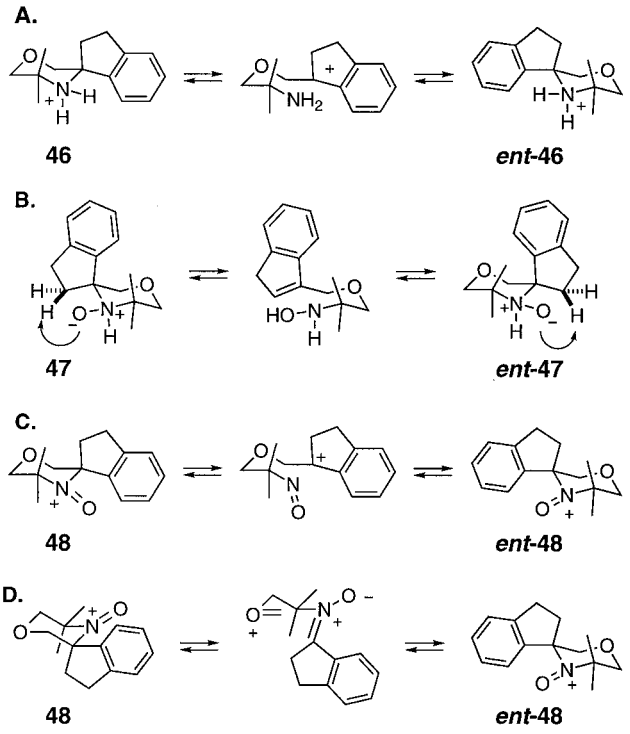
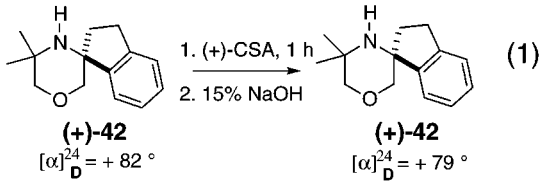


Figure 3. Four possible mechanisms for the racemization of nitroxide **43**.

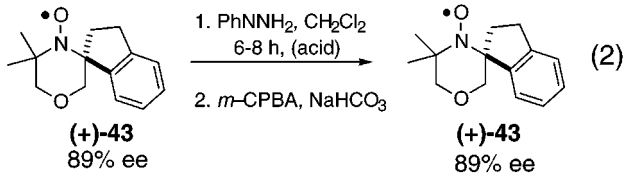
B, racemization takes place via the hydroxylamine and involves a reversible Cope and retro-Cope sequence. Hydroxylamine **47** is a likely intermediate in the oxidation of amine **42**, and Ciganek has shown that retro-Cope cyclizations can take place under very mild conditions.[21] Mechanism C involves solvolytic opening and closing of the *N*-oxo ammonium salt, an overoxidation product of the nitroxide. Mechanism D is based on a reversible Grob fragmentation of the same *N*-oxo ammonium salt **48**. This set of mechanisms appeared to be the most plausible routes for the racemization observed in the synthesis of optically pure nitroxide **43**.

To test for racemization of the morpholine salt, (+)-**42** was treated with CSA for 1 h at 25 °C, eq 1. Essentially no racemization was observed, and we conclude that racemization of the morpholine salt under the oxidation conditions is not feasible.



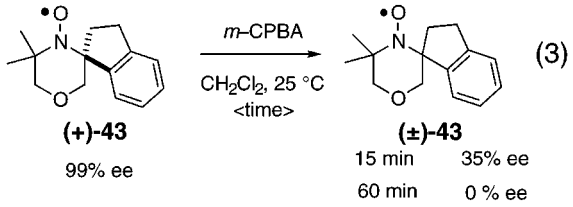
(1)

To test mechanism B the optically active nitroxide **43** was reduced to the hydroxylamine with phenylhydrazine.[22] The hydroxylamine was allowed to stand for several hours at 25 °C before reoxidation to the nitroxide with buffered *m*-CPBA. No racemization was observed under these conditions. The reaction was repeated with acetic acid present to see if mild acid promoted racemization of the hydroxylamine **47**, but once again no racemization was observed (eq 2). We concluded that the Cope/retro-Cope sequence was not taking place and that mechanism B could be removed from consideration.



(2)

Both of the remaining mechanistic proposals for racemization involve the *N*-oxo ammonium salt **48**. When optically pure nitroxide **43** was treated with commercial *m*-CPBA without a buffer, rapid racemization ensued. The optical purity was reduced to 35% ee in just 15 min, and complete racemization was observed in 60 min, eq 3. Both Cella and Ganem have shown that *m*-CPBA is



(3)

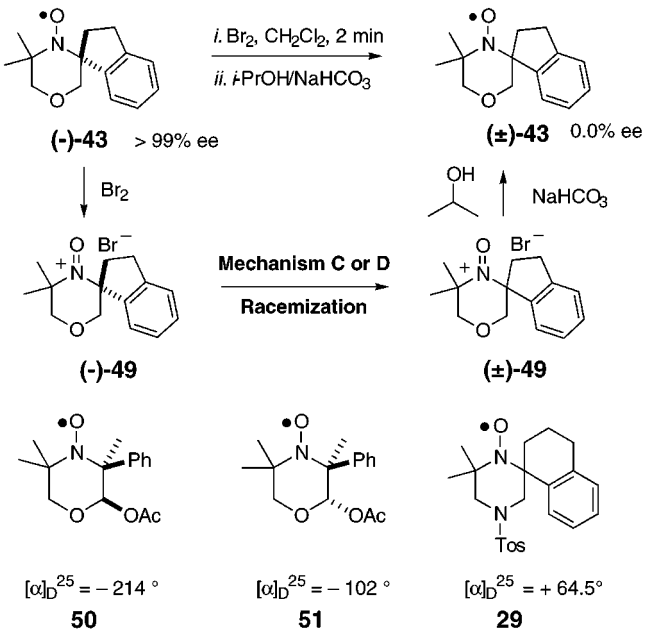
an effective bulk oxidant for TEMPO mediated oxidations of alcohols, where the active oxidant is an *N*-oxo ammonium salt.[23] Thus the most likely species involved in the racemization is an *N*-oxo ammonium salt. Nitroxides are known to reversibly disproportionate to hydroxylamine salts and *N*-oxo ammonium salts on treatment with acid.[24] We were concerned that acid might be a player in the racemization reaction. Optically pure nitroxide **43** was treated separately with 3-chlorobenzoic acid, acetic acid, and *p*-toluenesulfonic acid but showed no racemization after several hours at 25 °C. In contrast, base washed *m*-CPBA led to complete racemization of **43**. Thus the oxidant is necessary for the racemization but the acid is not.

How does aqueous sodium bicarbonate prevent racemization (Scheme 7)? The bicarbonate or water may simply add to the small quantities of *N*-oxo ammonium ion generated, thereby preventing it from catalyzing the racemization; vide infra. Protection of the *N*-oxo ammonium ion would also explain the following observation: addition of *m*-CPBA and MeOD led to neither deuterium incorporation nor racemization. The *N*-oxo ammonium ion would rapidly oxidize MeOD and, thus, have a much shorter lifetime and be protected from racemization.

A conclusive test for the intermediacy of the *N*-oxo ammonium ion in the racemization is shown in Scheme 8. Bromine is known to rapidly and quantitatively oxidize nitroxides to *N*-oxo ammonium salts.[25] Treatment of optically pure **43** with bromine immediately gave the bright orange *N*-oxo ammonium salt. Quenching this intermediate with buffered *i*-PrOH after only 2 min at 25 °C returned the racemic nitroxide **43**.[26] This racemization is much faster than with *m*-CPBA, which does not give the orange color of the *N*-oxo ammonium ion and presumably only produces it in low concentrations. Thus,

(23) (a) Cella, J. A.; Kelley, J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860−1862. (b) Ganem, B. *J. Org. Chem.* **1975**, *40*, 1998−2000.
(24) Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110−6114.
(25) Bobbitt, J. M.; Flores, C. L. *Heterocycles* **1988**, *27*, 509−533.
(26) *N*-Oxo ammonium salt **49** oxidizes *i*-PrOH to acetone. The resulting hydroxylamine is oxidized by a further 1 equiv of **49** to give nitroxide **43**.

Scheme 8



electron transfer would interconvert the *N*-oxo ammonium ion and nitroxide, and as a result, small amounts of the *N*-oxo ammonium ion would catalyze racemization of the nitroxide. These experiments establish the *N*-oxo ammonium ion as an intermediate in the racemization and are consistent with either mechanistic proposal C or D.

We favor mechanism C over mechanism D largely on the basis of circumstantial evidence. Unbuffered *m*-CPBA oxidations produce **50**, **51**, and **29** with no apparent racemization. If the Grob fragmentation were important, one might expect the *N*-oxo ammonium salt from **50** and **51** to fragment more rapidly than **49** because of the more effective stabilization of the oxonium ion. The *N*-tosyl nitroxide **29** could also participate in a Grob fragmentation, but racemization was not observed. In an effort to force the racemization, **29** was treated with bromine for 2 min and then quenched as described previously, but no racemization was observed. Of all of the nitroxides examined, indane **43** appears uniquely susceptible to oxidative racemization. The unusual reactivity of **43** is best attributed to the 1−2 orders of magnitude higher rates of solvolysis for cyclopentanes when compared with cyclohexanes or acyclic systems.[27]

Scope of the Bargellini Reaction. We have explored the scope of the Bargellini reaction for the synthesis of chiral morpholinones and piperazinones. Only acetone and cyclohexanone could be successfully coupled with diamine **16** in the key step. Most other ketones, especially aryl ketones, react sluggishly, if at all. However, reaction of amino alcohol **31** with ketones appears more general. This is evident from the fact that amino alcohol **31** reacts with acetophenone to furnish the corresponding morpholinone in good yields, while diamine **16** does not react at all. Highly enolizable ketones such as indanone do not react either with diamine **16** or amino alcohol **31** but spontaneously polymerize upon addition of base. Interesting chiral morpholinones and piperazinones may be synthesized by coupling complex amino alcohols or diamines with sterically less demanding ketones. These reactions proceed in excellent yields. The key coupling reaction is sensitive to the structure of the ketone component but tolerant to structural variations in the amino alcohol or diamine components.

(27) Brown, H. C.; Fletcher, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212−21.

Conclusions

We have adapted the Lai strategy, based on Bargellini couplings, for the synthesis of chiral nitroxides. Chiral piperazine, piperazinone, morpholine, and morpholinone nitroxides can prepared by these new routes. The Bargellini couplings are limited to a narrow range of ketones, but structural variations can be introduced in the amino alcohol or diamine components. A very convenient route to the diamine and amino alcohol precursors is based on condensations of nitroalkanes. The new chiral nitroxides available by this chemistry will be of interest as enantioselective oxidants, as traps for prochiral radicals, and in the preparation of new materials.

Indane nitroxide **43** is susceptible to racemization under oxidizing conditions. This unusual epimerization proceeds through the *N*-oxo ammonium salt. The facile racemization of nitroxides upon oxidation has not been previously reported.

Experimental Section[28]

5,5-Dimethyl-2-oxo-1-[(1*S*)-phenylethyl]spiro[piperazine-3,1′-cyclohexane] (18). A mixture of diamine **16** (193.4 mg 1.0 mmol), cyclohexanone (0.21 mL, 2.0 mmol), chloroform (0.12 mL, 1.5 mmol), powdered NaCN (3.1 mg, 0.06 mmol), benzyltriethylammonium chloride (5.0 mg, 0.02 mmol), and dichloromethane (0.5 mL) was stirred and cooled to 10 °C under argon. An aqueous solution of 50% NaOH was added dropwise with stirring so as to keep the temperature below 10 °C. The mixture was maintained at 10 °C overnight. The mixture was poured into a separatory funnel, and dichloromethane and water were added to dissolve the solids. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (10% MeOH/CH_2Cl_2, SiO_2) afforded 262.0 mg (87%) of piperazinone **18** as a white foam: IR (neat) 3313, 3030, 2932, 2857, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.22 (m, 5 H), 6.09 (q, J = 6.9 Hz, 1 H), 2.86 (d, J =

(28) **General experimental procedures:** Infrared spectra were recorded on a7 MIDAC Prospect FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Nicolet Omega 500, a Nicolet GN 500, a Nicolet QE 300, a Bruker 500, or a Bruker 300 spectrometer. Chemical shifts of the ^1H NMR and ^{13}C NMR spectra were referenced to residual solvent or to tetramethylsilane at 0.0 ppm. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*C*H), secondary (CH_2), and primary (CH_3) carbon atoms. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ. Mass spectra were determined on a AE2-MS 30, a PG 7070E-HF, a CG Analytical 7070E, or a Fisions autospec spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. Tetrahydrofuran, diethyl ether, and methylene chloride were dried by filtration through alumina according to the procedure described by Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520). All amine bases were distilled from calcium hydride and stored over potassium hydroxide. Benzene and acetonitrile were distilled from calcium hydride just prior to use. Capillary GC analysis was performed on a Hewlett-Packard model 6890 instrument equipped with a FID detector. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on E. Merck reagent silica gel 60 (230−400 mesh). Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using oven- or flame-dried glassware and standard syringe/septa techniques. All reagents were purchased from Aldrich Chemical Co. or Acros and were used as received, unless otherwise stated.

12.3 Hz, 1 H), 2.63 (d, J = 12.3 Hz, 1 H), 1.99−1.89 (m, 2 H), 1.68−1.52 (m, 7 H), 1.45 (d, J = 6.9 Hz, 3 H), 1.39−1.25 (m 2 H), 1.07 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 173.9, 140.1, 57.2, 48.6; *C*H, 128.3, 127.5, 127.2, 49.8; *C*H_2, 52.2, 36.6, 36.4, 31.1, 25.3, 20.9; *C*H_3, 27.8 (overlapping), 14.8. HRMS (CI, NH_3): found, m/z 300.2201 (M^+); $C_{19}H_{28}N_2O$ requires 300.2202.

5,5-Dimethyl-2-oxo-1-[(1*S*)-phenylethyl]spiro[piperazine-3,1′-cyclohexane]-*N*-oxyl (19). To a solution of **18** (190.4 mg, 0.63 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (330.3 mg, 1.90 mmol). The solution was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organics were washed (water, brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (20% EtOAc/hexanes, SiO_2) furnished 197.4 mg (99%) of **19** as a yellow solid: mp = 114−116 °C; IR (neat) 2975, 2939, 2928, 2861, 1648, 1496, 1486, 1454 cm^{-1}. HRMS (EI): found, m/z 315.2069 (M^+); $C_{19}H_{27}N_2O_2$ requires 315.2072. Anal. Calcd for $C_{19}H_{27}N_2O_2$: C, 72.35; H, 8.63; N,8.88. Found: C, 72.15; H, 8.53; N, 8.74

(1*S*)-*N*-(2-Nitro-2-phenylpropyl)-1-phenylethylamine (21). A 50 mL round-bottomed flask fitted with a reflux condenser was charged with (*S*)-α-methylbenzylamine (2.42 g, 0.02 mol). The flask was immersed in a water bath, the temperature of which was maintained at 15 °C. Aqueous formaldehyde (37%, 1.6 g, 0.02 mol) was added slowly to the flask with constant stirring over a period of 15 min. A highly viscous gel formed. After a further period of 5 min, 1-nitro-1-phenylethane (3.02 g, 0.02 mol) was added all at once and the mixture was stirred for 45 min without further cooling. Sodium sulfate (2 g) was added to the mixture and stirring was continued until most of the salt had dissolved. The contents were poured into a separatory funnel and allowed to stand for 15 days. The nonaqueous layer was separated from the aqueous layer and chromatographed (10% EtOAc/hexanes, SiO_2) to afford 3.4 g (60%) of the product as a 1:1.5 mixture of diastereomers that were inseparable: IR (mixture, neat) 3342, 3062, 3027, 2968, 2926, 2867, 1602, 1541 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer] δ 7.45−7.26 (m, 10 H), 3.86−3.79 (m, 1 H; overlapping), 3.69 (d, J = 13.2 Hz, 1 H), 2.82 (d, J = 13.2 Hz, 1 H), 2.02 (s, 3 H), 1.37 (d, J = 6.6 Hz, 3 H); ^{1}H NMR (300 MHz, $CDCl_3$) [minor isomer; characteristic peaks] δ 3.50 (d, J = 12.9 Hz, 1 H), 3.05 (d, J = 12.9 Hz, 1 H), 2.08 (s, 3 H), 1.35 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) [mixture] δ *C*, 145.2, 145.0, 138.6, 94.0, 93.8; *C*H, 128.8, 128.6, 128.4, 127.0, 126.6, 126.4, 125.3, 125.1, 58.6, 58.4; *C*H_2, 55.2, 55.1; *C*H_3, 24.6, 24.4, 22.8, 22.5. Anal. Calcd for $C_{17}H_{20}N_2O_2$ [mixture]: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.80; H, 6.81; N, 9.94.

(1*S*)-*N*-(2-Amino-2-phenylpropyl)-1-phenylethylamine (22). Raney nickel (200 mg) was washed sequentially with water (5 × 10 mL) and ethanol (5 × 10 mL). The catalyst was then rinsed into a 125 mL pressure reaction vessel containing nitroamine **21** (1.0 g, 3.5 mmol) in ethanol (10 mL). The reaction vessel was pressurized to 500 psi with H_2 and stirred at 60 °C for 16 h. The reaction mixture was cooled to room temperature, filtered through a plug of Celite, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH_2Cl_2, SiO_2) afforded 757.3 mg (85%) of product as a 1:1.5 mixture of diastereomers: IR (mixture, neat) 3365, 3311, 3083, 3060, 3026, 2967, 2925, 2895, 2867, 2833, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer] δ 7.53−7.19 (m, 10 H), 3.76−3.65 (m, 1 H; overlapping), 2.88 (d, J = 11.4 Hz, 1 H), 2.53 (d, J = 11.4 Hz, 1 H), 1.70 (br s), 1.41 (s, 3 H), 1.26 (d, J = 6.6 Hz, 3 H); ^{1}H NMR (300 MHz, $CDCl_3$) [minor isomer; characteristic peaks] δ 2.77 (d, J = 11.4 Hz, 1 H), 2.65 (d, J = 11.4 Hz, 1 H), 1.44 (s, 3 H), 1.31 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) [mixture] δ 147.5, 147.4, 145.7, 128.2, 128.1, 126.6, 126.5, 126.4, 126.2, 126.1, 125.2, 59.9, 59.7, 58.4, 58.3, 55.1, 55.0, 29.2, 29.1, 24.7, 24.3. Anal. Calcd for $C_{17}H_{22}N_2$ [mixture]: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.09; H, 8.52; N, 10.83.

(5*R*)- and (5*S*)-5-phenyl-3,3,5-trimethyl-1-[(1*S*)-phenylethyl]piperazin-2-one (23). A mixture of diamine **22** (566.0 mg 2.23 mmol), acetone (0.35 mL, 4.45 mmol), chloroform (0.27 mL, 3.34 mmol), powdered NaCN (7.0 mg, 0.13 mmol), benzyltriethylammonium chloride (10.0 mg, 0.04 mmol), and dichloromethane (1.2 mL) was stirred and cooled to 0 °C under argon. An aqueous solution of 50% NaOH was added dropwise with stirring so as to keep the temperature below 10 °C. The mixture was maintained at 10 °C overnight. The mixture was then poured into a separatory funnel, and dichloromethane and water were added to dissolve the solids. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and concentrated. Crude ^{1}H NMR indicated a 1:1 mixture of starting material and product. The crude mixture was resubmitted to the reaction conditions and worked up as before. Purification by flash chromatography (50% EtOAc/hexanes, SiO_2) afforded 232.0 mg of the minor diastereomer and 427.9 mg of the major diastereomer, which corresponds to an overall yield of 92%. The minor diastereomer was recrystallized from hexanes. Major diastereomer: $[\alpha]^{23}_D$ −130.5° (*c*, 1.14, $CHCl_3$); IR (neat) 3318, 3086, 3060, 3030, 2975, 2930, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.14 (m, 10 H), 6.17 (q, J = 6.9 Hz, 1 H), 3.23 (s, 2 H) 1.57 (d, J = 6.9 Hz, 3 H), 1.49 (s, 3 H), 1.42 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 173.7, 145.8, 139.6, 55.6, 53.9; *C*H, 128.3, 127.9, 127.5, 127.3, 126.5, 125.5, 49.6; *C*H_2, 50.9; *C*H_3, 30.0, 29.3, 14.8. Minor diastereomer: mp = 83−85 °C; $[\alpha]^{23}_D$ +14.83° (*c*, 2.04, MeOH); IR (neat) 3292, 2982, 2932, 1625, 1488, 1439, 1371, 1312, 1166, 869 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.20 (m, 10 H), 6.11 (q, J = 7.2 Hz, 1 H), 3.38 (d, J = 12.6 Hz, 1 H), 3.08 (d, J = 12.6 Hz, 1 H), 1.49 (s, 3 H), 1.38 (d, J = 7.2 Hz, 3 H), 1.34 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 146.9, 139.9, 128.4, 128.2, 127.8, 127.6, 126.9, 125.5, 55.7, 54.4, 51.1, 50.0, 30.0, 29.6, 28.5, 15.0. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.38; H, 7.89; N, 8.51.

1-Nitro-1-{[*N*-(1*S*)-phenylethyl]aminomethyl}tetralin. A 50 mL round-bottomed flask fitted with a reflux condenser was charged with (*S*)-α-methylbenzylamine (2.1 g, 18 mmol). The flask was immersed in a water bath, the temperature of which was maintained at 15 °C. Aqueous formaldehyde (37%, 1.4 g, 18 mmol) was added slowly to the flask with constant stirring over a period of 15 min. A highly viscous gel formed. After a further period of 5 min, 1-nitrotetralin (3.1 g, 18 mmol) was added all at once and the mixture was stirred for 45 min without further cooling. Sodium sulfate (2 g) was added to the mixture, and stirring was continued until most of the salt had dissolved. The contents were poured into a separatory funnel and allowed to stand for 5 days. The nonaqueous layer was separated from the aqueous layer and chromatographed (10% EtOAc/hexanes, SiO_2) to afford 4.3 g (77%) of the product as a 1:1.3 mixture of diastereomers that were inseparable: IR (mixture, neat) 3344, 3062, 3026, 2960, 2872, 1603, 1538 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer] δ 7.38−7.09 (m, 9 H), 3.82−3.73 (m, 1 H; overlapping), 3.59 (d, J = 13.5 Hz, 1 H), 2.73 (d, J = 13.5 Hz, 1 H), 2.95−2.77 (m, 1 H; overlapping), 2.67−2.51 (m, 3 H; overlapping), 2.01−1.91 (m, 1 H; overlapping), 1.63 (bs, 1 H); 1.62−1.46 (m, 1 H; overlapping); 1.36 (d, J = 6.6 Hz, 3 H); ^{1}H NMR (300 MHz, $CDCl_3$) [minor isomer; characteristic peaks] δ 3.43 (d, J = 13.2 Hz, 1 H), 3.02 (d, J = 13.2 Hz, 1 H), 1.31 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) [mixture] δ 145.2, 145.1, 138.3, 137.9, 132.7, 132.2, 129.5, 129.4, 128.9, 128.8, 128.4, 128.3, 127.0, 126.9, 126.7, 126.5, 93.5, 92.7, 58.6, 58.5, 54.8 (overlapping), 31.5, 30.9, 29.4, 29.3, 24.7, 24.4, 19.6, 19.4. Anal. Calcd for $C_{19}H_{22}N_2O_2$ [mixture]: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.70; H, 7.20; N, 9.05.

1-Amino-1-{[*N*-(1*S*)-phenylethyl]aminomethyl}tetralin (25). Raney nickel (200 mg) was washed sequentially with water (5 × 10 mL) and ethanol (5 × 10 mL). The catalyst was then rinsed into a 125 mL pressure reaction vessel containing the nitroamine (2.0 g, 6.8 mmol) in ethanol (20 mL). The reaction vessel was pressurized to 500 psi with H_2 and stirred at 50 °C for 4 h. The reaction mixture was cooled to

room temperature, filtered through a plug of Celite, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH_2Cl_2, SiO_2) afforded 1.4 g (77%) of product as an inseparable mixture of diastereomers: ^{13}C NMR (75 MHz, $CDCl_3$) [mixture] δ 145.6, 140.7, 137.1, 136.9, 136.8, 129.0, 128.9, 128.4, 128.2, 127.1, 126.6, 126.4, 126.2, 126.1, 126.0, 125.0, 1125.8, 60.2, 58.6, 58.5, 56.9, 54.7, 54.4, 34.9, 34.5, 29.9, 29.7, 24.4, 24.3, 19.3, 19.2. The diamine **25** was used without further characterization.

3′,3′-Dimethyl-2′-oxo-1′-[(1*S*)-phenylethyl]spiro[tetralin-1,5′-piperazine] (26). A mixture of diamine **25** (1.1 g 3.9 mmol), acetone (0.6 mL, 7.7 mmol), chloroform (0.46 mL, 5.8 mmol), powdered NaCN (7.0 mg, 0.13 mmol), benzyltriethylammonium chloride (10.0 mg, 0.04 mmol), and dichloromethane (2 mL) was stirred and cooled to 0 °C under argon. An aqueous solution of 50% NaOH was added dropwise with stirring so as to keep the temperature below 10 °C. The mixture was maintained at 10 °C overnight. The mixture was then poured into a separatory funnel, and dichloromethane and water were added to dissolve the solids. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and concentrated. Crude ^1H NMR indicated a mixture of starting material and product. The crude mixture was resubmitted to the reaction conditions and worked up as before. Purification by flash chromatography (50% EtOAc/hexanes, SiO_2) afforded 1.3 g (96%) of the piperazinone as a 1:1.3 mixture of diastereomers: IR (mixture, neat) 3319, 3061, 3029, 2972, 2933, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) [major isomer] δ 7.55−7.02 (m, 9 H), 6.14 (q, J = 6.9 Hz, 1 H), 3.05 (d, J = 15.7 Hz, 1 H), 3.00 (d, J = 15.6 Hz, 1 H), 2.86−2.70 (m, 2 H), 2.19−2.13 (m, 1 H; overlapping), 1.97−1.88 (m, 1 H), 1.81−1.65 (m, 2 H), 1.54−1.44 (m, 10 H); ^1H NMR (300 MHz, $CDCl_3$) [minor isomer; characteristic peaks] δ 6.18 (q, J = 7.1 Hz, 1 H), 3.33 (d, J = 12.5 Hz, 1 H), 2.96 (d, J = 12.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) [mixture] δ 173.5, 173.0, 140.8, 140.5, 139.8, 139.7, 137.5, 137.3, 128.7, 128.6, 128.4, 128.2, 127.9, 127.5, 127.2, 127.1, 126.9, 126.0, 125.9, 55.9, 55.4, 53.7, 50.9, 49.7, 49.6, 49.5, 34.2, 34.1, 32.4, 32.1, 29.9, 29.8, 29.5, 19.8, 19.1, 14.9, 14.8. HRMS (CI, *i*-C_4H_{10}): found, *m*/*z* 348.2189 (M^+); $C_{23}H_{28}N_2O$ requires 348.2210.

3′,3′-Dimethyl-1′-[(1*S*)-phenylethyl]spiro[tetralin-1,5′-piperazine] (27). A 50 mL two-neck round-bottomed flask fitted with a reflux condenser was charged with a 1.6 M solution of $LiAlH_4$ in THF (2.3 mL, 3.6 mmol) and cooled to 0 °C. To this was added a solution of piperazinone **26** (898 mg, 2.6 mmol) in THF (5 mL). The reaction was allowed to stir at 0 °C for 20 min and refluxed for 6 h. The reaction mixture was cooled to 0 °C and quenched by sequential addition of H_2O (1 mL), 15% NaOH (1 mL), and H_2O (3 mL). The mixture was filtered through a plug of Celite, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over Na_2SO_4 and concentrated in vacuo to afford 856 mg (98%) of **27** as a mixture of diastereomers which was used without further purification.

Resolution. To a solution of piperazine **27** (1.98 g, 5.7 mmol, mixture of diastereomers) in 20 mL of EtOAc was added a solution of (*R*)-(−)-camphorsulfonic acid (1.51 g, 6.5 mmol) in 5 mL of EtOAc and 1 mL of MeOH. The solution was concentrated to ca. 5 mL under reduced pressure. A solid crashed out. The solid was dissolved in 10 mL of EtOAc and 1 mL of MeOH. The mixture was allowed to stand at room temperature overnight. The crystals that crashed out were filtered out and washed with cold EtOAc. The solid was dissolved in 5 mL of CH_2Cl_2 and washed with 1 N NaOH solution (3 × 5 mL), H_2O (3 × 5 mL), and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 546 mg of diastereomerically pure piperazine **27** as a colorless oil: $[\alpha]^{23}_D$ −26.3° (*c*, 1.0, $CHCl_3$); IR (neat) 3325, 3082, 3060, 3025, 2969, 2926, 2867, 2835, 2808, 2767, 2751, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 1 H), 7.45−7.04 (m, 8 H), 3.45 (q, J = 6.6 Hz, 1 H), 2.98−2.65 (m, 5 H), 2.12 (d, J = 10.5 Hz, 1 H), 2.02 (d, J = 11.4 Hz, 1 H),1.90−1.86 (m, 1 H), 1.75−1.66 (m, 1 H), 1.53 (s, 3 H), 1.46 (d, J = 6.6 Hz, 3 H), 1.46 (m, 1 H), 1.23 (s, 3 H), 1.05 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 145.1, 143.2, 138.0, 55.9, 50.4; *C*H, 128.3, 128.0 (overlapping), 127.4, 126.6, 126.2, 125.5, 64.1; *C*H_2, 62.0, 61.6, 36.4, 29.9, 20.6; *C*H_3, 32.3, 30.2, 20.1. Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.70; H, 9.20; N, 8.41.

(+)-6′,6′-Dimethylspiro[tetralin-1,2′-piperazine]. Diastereomerically pure piperazine **27** (187.4 mg, 0.6 mmol) was dissolved in methanol (5 mL), and the solution was hydrogenated at room temperature and 50 psi in the presence of Pearlman's catalyst (25 mg) for 6 h. The reaction mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH_2Cl_2, SiO_2) afforded 102.1 mg (79%) of the product as a colorless oil: $[\alpha]^{23}_D$ +52.7° (*c*, 0.95, $CHCl_3$); IR (neat) 3050, 3012, 2929, 2865, 2837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 1 H), 7.18−7.10 (m, 2 H), 7.01 (d, J = 7.4 Hz, 1 H), 3.02 (d, J = 12.8 Hz, 1 H), 2.84−2.63 (m, 6 H), 1.91−1.89 (m, 2 H), 1.69−1.63 (m, 3 H), 1.32 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 138.2, 128.7, 128.0, 126.9, 126.0, 54.7, 54.2, 52.8, 48.9, 35.5, 32.0, 29.7, 28.7, 20.4. HRMS (CI, NH_3): found, *m*/*z* 230.1786 (M^+); $C_{15}H_{22}N_2$ requires 230.1783.

(+)-3′,3′-Dimethyl-1′-[(4-methylphenyl)sulfonyl]spiro-[tetralin-1,5′-piperazine] (28). To a solution of piperazine obtained from the previous step (125.6 mg, 0.5 mmol) in dry CH_2Cl_2 (4 mL) were added Et_3N (87 μL, 0.6 mmol) and a solution of *p*-toluenesulfonyl chloride (114.5 mg, 0.4 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of saturated $NaHCO_3$ (3 mL). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, concentrated, and chromatographed (10% EtOAc/hexanes) to afford 199.8 mg (95%) of (+)-**28** as a yellowish-white foam: $[\alpha]^{23}_D$ +97.3° (*c*, 0.89, $CHCl_3$); IR (neat) 3332, 3062, 2961, 2927, 2865, 2256, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.60 (m, 1 H), 7.61 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 7.15−7.03 (m, 3 H), 3.76 (d, J = 11.4 Hz, 1 H),), 3.56 (d, J = 11.1 Hz, 1 H), 2.85−2.74 (m, 3 H), 2.43 (s, 3 H), 2.27−2.21 (m, 2 H), 1.98−1.94 (m, 1 H), 1.86−1.63 (m, 3 H), 1.45 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 141.0, 138.5, 133.8, 129.6, 128.7, 128.1, 127.4, 126.9, 125.8, 56.8, 55.6, 54.8, 50.3, 35.6, 31.4, 29.7, 29.0, 21.4, 20.5. HRMS (CI, NH_3): found, *m*/*z* 385.1940 (M + H^+); $C_{22}H_{28}N_2O_2S$ + H requires 385.1949.

(+)-3′,3′-Dimethyl-1′-[4-methylphenylsulfonyl]spiro-[tetralin-1,5′-piperazine]-*N*-oxyl [(+)-29]. To a solution of (+)-**28** (178.3 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) was added *m*-CPBA (152.5 mg, 0.88 mmol). The solution was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organics were washed (water, brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (15% EtOAc/hexanes, SiO_2) furnished 183.8 mg (100%) of (+)-**29** as a pink foam: $[\alpha]^{23}_D$ +64.5° (*c*, 0.97, $CHCl_3$); IR (neat) 3022, 2995, 2937, 2866, 1598 cm^{-1}. Anal. Calcd for $C_{22}H_{27}N_2O_3S$: C, 66.14; H, 6.81; N,7.01. Found: C, 66.40; H, 7.00; N, 6.77. HRMS (CI, *i*-C_4H_{10}): found, *m*/*z* 399.1743 (M^+); $C_{22}H_{27}N_2O_3S$ requires 399.1742.

3,5,5-Trimethyl-2-oxo-3-phenylmorpholine (33). 2-Amino-2,2-dimethylethanol (**31**) (1.0 g, 11.22 mmol, 1.0 equiv), benzyltriethylammonium chloride (13 mg, 0.056 mmol, 0.005 equiv), and 2.6 mL of acetophenone (22.43 mmol, 2.0 equiv) were dissolved in 122 mL of CH_2Cl_2 and cooled to 0 °C. Powdered NaOH (2.2 g, 56.1 mmol, 5 equiv) was added in small portions, keeping the reaction temperature below 5 °C. After the addition, the reaction was warmed to 10 °C and stirred at this temperature for 12 h. The resulting white suspension was filtered using a Büchner funnel, and the filter cake was rinsed with acetone. The white powder was suspended in 250 mL of MeOH and filtered, and the solvent was removed under reduced pressure to give 2.5 g of carboxylate salt **32**. The salt was refluxed with 12 M HCl for 15 h, and the acid was removed under reduced pressure to give a white

solid. The solid was azeotropically dried by refluxing in 150 mL of toluene using a Dean−Stark trap. The toluene was removed under reduced pressure and replaced with Et_3N (150 mL). The suspension was sparged with argon and refluxed for 4 h. After being cooled to room temperature, the suspension was filtered and concentrated under reduced pressure to give the crude morpholinone (±)-**33**. The solid was recrystallized from hexane to give 1.4 g (6.35 mmol, 57%) of morpholinone (±)-**33** as a white crystalline solid: mp = 99−100 °C; IR (KBr) 3464, 3351, 3058, 2961, 1741, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (ddd, J = 8.0, 1.5, 1.0 Hz, 2 H), 7.36 (dddd, J = 8.0, 7.5, 1.5, 1.0 Hz, 2 H), 7.28 (ddd, J = 7.5, 1.5, 1.5 Hz, 1 H), 3.78 (d, J = 12.0 Hz, 1 H), 3.74 (d, J = 12.0 Hz, 1 H), 1.50 (s, 3 H), 1.34 (s, 1 H), 1.30 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 143.1, 128.8, 127.6, 125.1, 73.4, 61.6, 51.0, 30.9, 28.6, 27.2. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.34; H, 7.67; N, 6.42.

3,5,5-Trimethyl-2-oxo-3-phenylmorpholine-*N*-oxyl (34). To a 0.03 M solution of morpholone (±)-**33** (62 mg, 0.283 mmol, 1.0 equiv) in CH_2Cl_2 was added *m*-CPBA (97.0 mg, 0.562 mmol, 2.0 equiv). The resulting dark yellow solution was allowed to stir at room temperature overnight. The reaction mixture was quenched with 10% K_2CO_3 solution, extracted (3 × CH_2Cl_2), washed (H_2O, brine), dried (Na_2SO_4), and concentrated under reduced pressure to give a dark yellow oil. Chromatography (flash, SiO_2, 20% EtOAc/hexanes) gave 58.6 mg (0.250 mmol, 88%) of (±)-**34** as a dark yellow oil: IR (neat) 3055, 2980, 1760, 1373, 1366, 1114, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ very broad unresolved peaks indicative of paramagnetic radical. HRMS (EI): found, m/z 243.1125 (M^+); $C_{13}H_{16}NO_3$ requires 243.1130. Anal. Calcd for $C_{13}H_{16}NO_3$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.55; H, 6.81; N, 5.95.

3,5,5-Trimethyl-3-phenyl-2-thionomorpholine (35). Lawesson's reagent (616 mg, 1.52 mmol, 1.0 equiv) was added to racemic morpholone **33** (336 mg, 1.52 mmol, 1.0 equiv) in 7.6 mL of toluene, and the resulting suspension was heated to reflux. After 1 h, the reaction was cooled to room temperature. The stir bar was removed from the flask, and 1 g of SiO_2 was added. The solvent was removed under reduced pressure, and the SiO_2 was loaded onto a flash column. Chromatography (flash, SiO_2, 0−30% EtOAc/hexanes) gave 173 mg (0.732 mmol, 48%) of **35** as a clear, colorless oil: R_f 0.50 (20% EtOAc/hexanes); IR (neat) 3342, 3060, 2971, 1598, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.95, 1.5, Hz, 2 H), 7.23−7.36 (m, 3 H), 3.90 (d, J = 11.1 Hz, 1 H), 3.77 (d, J = 11.1 Hz, 1 H), 1.61 (s, 3 H), 1.39 (bs, 1 H), 1.25 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 225.1, 143.4, 129.0, 127.8, 125.8, 77.8, 67.5, 52.4, 35.5, 29.4, 27.7. HRMS (CI, NH_3): found, m/z 236.1110 (M + H^+); $C_{13}H_{17}NOS$ + H requires 236.1109.

2-Hydroxy-3,5,5-trimethyl-3-phenylmorpholine. Morpholone (±)-**33** (0.50 g, 2.27 mmol, 1.0 equiv) was dissolved in 2.5 mL of Et_2O and cooled to −20 °C. A 1.0 M solution of DIBAL-H in hexane (2.72 mL, 2.72 mmol, 1.2 equiv) was added dropwise by syringe. After 30 min, the reaction was quenched by sequential addition of MeOH (0.7 mL) and 30% NaK tartrate solution. The mixture was warmed to room temperature, extracted (3 × EtOAc), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a white solid. The solid was recrystallized from 15:1 CH_2Cl_2/hexanes to give 0.453 g (2.05 mmol, 90%) of the lactol as a 5.4:1 mixture of C2 epimers: mp (5.4:1 mixture) = 128−131 °C; IR (KBr, mixture) 3366, 2969, 1446, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) [major isomer] δ 7.62 (dd, J = 8.1, 1.2 Hz, 2 H), 7.31 (dd, J = 7.2, 8.2 Hz, 2 H), 7.23 (dd, J = 7.2, 1.2 Hz, 1 H); 5.29 (s, 1 H), 3.83 (d, J = 11.1 Hz, 1 H), 3.27 (d, J = 11.1 Hz, 1 H), 1.42 (s, 3 H), 1.17 (s, 3 H), 0.74 (s, 3 H); ^1H NMR (500 MHz, $CDCl_3$) [minor isomer, characteristic peaks] δ 5.04 (s, 1 H), 3.81 (d, J = 11.1 Hz, 1 H), 3.40 (d, J = 11.1 Hz, 1 H), 1.54 (s, 3 H), 1.22 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR [125 MHz, $CDCl_3$, major (2,3-trans)] δ 146.6, 127.9, 126.4, 126.2, 94.6, 71.0, 56.9, 48.8, 28.4, 27.5, 26.4; ^{13}C NMR [125 MHz, $CDCl_3$, minor (2,3-cis)] δ 145.5, 128.0, 126.6, 126.3, 98.2, 71.4, 57.1, 48.9, 29.6, 28.4, 28.2. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found (mixture): C, 70.66; H,8.62; N, 6.38.

***cis*- and *trans*-3,5,5-Trimethyl-3-phenyl-2-thiophenylmorpholine (37).** To a solution of lactol obtained in the previous step (0.20 g, 0.90 mmol, 1.0 equiv, 5.4:1 mixture of C2 epimers) and diphenyl disulfide (0.216 g, 0.989 mmol, 1.1 equiv) in 5.0 mL of CH_3CN was added Bu_3P (0.266 mL, 0.989 mmol, 1.1 equiv). After being stirred at room temperature overnight, the reaction was quenched with 1 M NaOH and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted (3 × Et_2O). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 253 mg (0.804 mmol, 89%) of **37** in a 13:1 ratio of C2 epimers. Chromatography (flash, SiO_2, 10−30% EtOAc/hexanes) gave 17 mg (0.054 mmol, 6.0%) of the minor diastereomer and 226 mg (0.719 mmol, 80%) of the major diastereomer as clear, colorless oils. Major diastereomer: IR (neat) 3307, 3059, 2963, 1583, 1479, 1284, 1061 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2 H), 7.45 (d, J = 7.5 Hz, 2 H), 7.34 (t, J = 7.5 Hz, 2 H), 7.29 (t, J = 7.5, 2 H), 7.23 (m, 2 H), 5.23 (s, 1 H), 3.99 (d, J = 11.5 Hz, 1 H), 3.41 (d, J = 11.5 Hz, 1 H), 1.67 (s, 3 H), 1.54 (bs, 1 H), 1.17 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145. 4, 136.4, 130.7, 128.9, 127.8, 126.8, 126.7(2), 94.6, 74.5, 58.1, 49.1, 31.4, 28.9, 27.7. Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47. Found: C, 72.94; H, 7.49; N, 4.38.

3,5,5-Trimethyl-3-phenylmorpholine via Raney Nickel Reduction of Thionomorpholone 35. Raney nickel (0.37 g, Aldrich) was washed with DI water until the pH was 7.0 and then further washed with absolute EtOH (10 × 10 mL). The EtOH suspension was transferred to an oven dried flask. The catalyst was placed under an argon atmosphere and washed with anhydrous Et_2O (3 × 10 mL). A solution of thionomorpholone **35** (168 mg, 0.714 mmol) in 2 mL of Et_2O was added to the dry catalyst via cannula, and the resulting suspension was stirred at room temperature for 1.5 h. An additional 0.4 g of Raney nickel was added since TLC analysis indicated incomplete reaction. After 15 min, the reaction mixture was filtered, and the solvent was removed under reduced pressure. Chromatography (flash, SiO_2, 30% EtOAc/hexanes) gave 70 mg (0.343 mmol, 48%) of the morpholine as a colorless oil: R_f 0.27 (50% EtOAc/hexanes); IR (neat) 3317, 3060, 2964, 2964, 1462, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 2 H), 7.32 (dd, J = 7.5, 7.0 Hz, 2 H), 7.22 (dd, J = 7.0, 1.0 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 3.49 (d, J = 10.8 Hz, 1 H), 3.38 (d, J = 12.0 Hz, 1 H), 3.27 (d, J = 10.8 Hz, 1 H), 1.40 (bs, 1 H), 1.26 (s, 3 H), 1.05 (s, 3 H), 0.66 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 127.9, 126.2 (2), 78.0, 74.7, 53.1, 49.4, 30.4, 28.5, 26.6.

3,5,5-Trimethyl-3-phenylmorpholine via Li/NH_3 Reduction of Thioacetal 37. Thioacetal **37** (197 mg, 0.626 mmol, 1.0 equiv) was dissolved in 4 mL of THF and cooled to −78 °C. Ammonia (ca. 10 mL) was condensed into the flask, and lithium metal (43 mg, 6.26 mmol, 10 equiv) was added to the solution. After the reaction mixture turned blue in color, it was allowed to proceed for an additional 2 min and quenched via dropwise addition of MeOH. The ammonia was allowed to evaporate, and the resulting residue was dissolved in water and Et_2O. The layers were separated, and the aqueous layer was extracted (3 × Et_2O). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (flash, SiO_2, 30% EtOAc/hexanes) gave 104 mg (0.507 mmol, 81%) of the morpholine as a clear, colorless oil.

3,5,5-Trimethyl-3-phenylmorpholine-*N*-oxyl (36). To a 0.05 M solution of morpholine (46.2 mg, 0.225 mmol, 1.0 equiv) in CH_2Cl_2 was added *m*-CPBA (77.7 mg, 0.45 mmol, 2.0 equiv) in one portion. The resulting orange solution was allowed to stir at room temperature for 30 min. The reaction mixture was quenched with 10% K_2CO_3 solution, extracted (3 × CH_2Cl_2), washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a red oil. Chromatography (flash, SiO_2, 10% Et_2O/pentane) gave 48.5 mg (0.220 mmol, 98%) of **36** as a red oil: R_f 0.24 (20% EtOAc/hexanes); IR (neat) 3060, 2974, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) broad unresolved peaks indicative of paramagnetic radical. HRMS (EI): found, m/z 220.1339 (M^+); $C_{15}H_{20}NO_4$ requires

220.1337. Anal. Calcd for $C_{13}H_{18}NO_2$: C, 70.88; H, 8.24; N, 6.36. Found: C, 70.66; H, 8.34; N, 6.31.

1-(Hydroxymethyl)-1-nitroindane. To a 0.4 M solution of 1-nitroindane **38** (2.30 g, 14.1 mmol, 1.0 equiv) in THF were added paraformaldehyde (0.85 g, 28.2 mmol, 2.0 equiv) and 0.30 mL of a 25 wt % solution of NaOMe in MeOH (5.20 mmol, 0.37 equiv). The resulting suspension was heated to reflux. After 3 h at reflux, the solution was cooled to room temperature, poured into 1 M HCl, extracted (3 × Et_2O), washed (H_2O, pH 7.0 buffer, brine), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Chromatography (MPLC, SiO_2, 20% EtOAc/hexanes) gave 2.43 g (12.56 mmol, 89%) of the desired alcohol as a light yellow oil: R_f 0.17 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.48 (m, 4 H), 4.53 (d, J = 12.3 Hz, 1 H), 3.97 (d, J = 12.3 Hz, 1 H), 3.23−3.35 (m, 1 H), 2.95−3.08 (m, 2 H), 2.5−2.61 (m, 1 H), 2.28 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 137.0, 130.0, 127.2, 125.4, 124.2, 105.0, 66.6, 33.6, 30.2. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.93; H, 5.94; N, 6.83.

1-Amino-1-(hydroxymethyl)indane [(±)-39]. Raney nickel (0.20 g, Aldrich) was washed with DI water until the pH was 7.0 and then further washed with EtOH (10 × 15 mL). The catalyst was then rinsed into a 125-mL pressure reaction vessel containing the nitro alcohol (0.775 g, 4.01 mmol, 1.0 equiv) using absolute EtOH (20 mL). The reaction vessel was pressurized to 500 psi with H_2 and heated to 55 °C. After being vigorously stirred for 12 h, the reaction mixture was cooled to room temperature and depressurized. The mixture was filtered through Celite and concentrated under reduced pressure to give a clear syrup. Chromatography (flash, SiO_2, 1% NH_4OH and 5% MeOH in $CHCl_3$) gave a white solid which was recrystallized from CH_2Cl_2 to give 0.652 g (3.93 mmol, 98%) of amine (±)-**39** as a white crystalline solid: mp = 102−103 °C; IR (neat) 3331, 3091, 2827, 1604, 1012 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.31 (m, 1 H), 7.22−7.24 (m, 3 H), 3.54 (d, J = 11.0 Hz, 1 H), 3.51 (d, 11.0 Hz, 1 H), 2.94 (ddd, J = 16.0, 9.0, 3.5 Hz, 1 H), 2.87 (ddd, J = 16.0, 8.5, 8.0 Hz, 1 H), 2.38 (ddd, J = 13.0, 8.0, 3.5 Hz, 1 H), 2.15 (bs, 3 H), 1.85 (ddd, J = 13.0, 9.0, 8.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 143.1, 127.9, 126.6, 125.0, 122.9, 68.3, 65.5, 38.2, 29.3. HRMS (CI): found, m/z 164.1072 (M^+); $C_{10}H_{13}NO$ requires 164.1074. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.77; H, 7.91; N, 8.36.

3′,3′-Dimethyl-2′-oxospiro[indan-1,5′-morpholine] [(±)-40]. Racemic amino alcohol **39** (0.213 g, 1.30 mmol, 1.0 equiv), benzyltriethylammonium chloride (3 mg, 0.013 mmol, 0.01 equiv), and 1.0 mL of acetone (13 mmol, 10 equiv) were dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C. Powdered NaOH (0.26 g, 6.5 mmol, 5 equiv) was added in one portion, and the reaction was maintained at a temperature between 0 and 6 °C for 6 h. After 6 h, the reaction was allowed to slowly warm to room temperature over a 12 h period. The resulting white suspension was filtered using a Büchner funnel, and the resulting filter cake was rinsed with CH_2Cl_2. The white powder was dissolved in 50 mL of MeOH and filtered, and the solvent was removed under reduced pressure to give 0.352 g (quant) of the carboxylate salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.38 (m, 1 H), 7.15 (m, 3 H), 3.47 (d, J = 9.5 Hz, 1 H), 3.32 (m, 1 H), 3.27 (d, J = 9.5 Hz, 1 H), 2.89−2.94 (m, 1 H), 2.78−2.85 (m, 1 H), 2.20−2.26 (m, 1 H), 2.13−2.17 (m, 1 H), 1.26 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 187.3, 148.9, 143.4, 128.4, 126.9, 125.3, 125.6, 71.4, 67.3, 60.2, 34.4, 31.9, 30.9, 26.0.

The crude carboxylate salt (0.352 g, 1.3 mmol) was suspended in 50 mL of toluene and sparged with argon for 15 min. (+)-Camphorsulfonic acid (1.37 g, 5.89 mmol, 4.5 equiv) was added to the suspension, and the reaction mixture was refluxed for 10 h. The suspension was then poured into saturated $NaHCO_3$, extracted (3 × EtOAc), washed (brine), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Chromatography (flash, SiO_2, 17% EtOAc/hexanes) gave a light orange solid that was recrystallized from hexanes to give 0.20 g (0.865 mmol, 66%) of the desired morpholinone (±)-**40** as a white solid: R_f 0.18 (20% EtOAc/hexane); mp = 86.0−86.5 °C; HPLC (normal phase analytical, 96% Hex/IPA, 0.5 mL/min, obs at 205, 230, 265 nm) t_R = 16.6 min, 100% purity; HPLC (chiralpak-AD, 96% Hex/IPA, 0.5 mL/min, obs at 205m 239m 265 nm) t_R = 17.3, 18.8 min; 1:1 ratio at all three wavelengths; IR (neat) 3313, 2941, 1723, 1221, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 6.0 Hz, 1 H), 7.22−7.27 (m, 3 H), 4.33 (d, J = 11.0 Hz, 1 H), 4.18 (d, J = 11.0 Hz, 1 H), 3.0 (ddd, J = 16.0, 9.0, 2.0 Hz, 1 H), 2.88 (ddd, J = 15.0, 8.0, 8.0 Hz, 1 H), 2.57 (ddd, J = 12.0, 8.0, 2.0 Hz, 1 H), 1.94 (ddd, J = 12.0, 9.0, 8.0 Hz, 1 H), 1.54 (s, 3 H), 1.51 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 144.5, 142.7, 128.6, 126.9, 125.0, 123.3, 73.2, 64.0, 55.4, 38.4, 31.0, 30.1, 29.2. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.30; N, 6.07.

***cis*- and *trans*-(2′*S**,5′*S**)-2′-acetoxy-3′,3′-dimethylspiro-[indan-1,5′-morpholine].** Morpholinone (±)-**40** (150 mg, 0.648 mmol, 1.0 equiv) was dissolved into 10 mL of Et_2O and cooled to 0 °C. A 0.8 M solution of DIBAL-H in hexane (1.5 mL, 1.2 mmol, 1.85 equiv) was added dropwise by syringe. After 10 min, the reaction was quenched by sequential addition of MeOH (1.0 mL) and 30% NaK tartrate solution. The mixture was warmed to room temperature, extracted (3 × EtOAc), washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid. The white solid was dissolved in 10 mL of CH_2Cl_2 and treated with Et_3N (0.46 mL, 3.27 mmol, 5.0 equiv), Ac_2O (0.122 mL, 1.30 mmol, 2.0 equiv), and DMAP (ca. 2 mg). After being stirred for 12 h, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted (3 × CH_2Cl_2), washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (flash, SiO_2, 20% EtOAc/hexanes) gave 70.2 mg (0.25 mmol, 39%) of the early eluting trans acetoxy acetal as a colorless oil, 40 mg (0.123 mmol, 18%) of the late eluting cis isomer as a white solid, and 37.5 mg (0.117 mmol, 18%) of the bis(acetate) as a colorless oil. When the DIBAL-H reduction was done at −78 °C, overreduction was not a problem.

Trans isomer: R_f 0.16 (20% EtOAc in hexane); IR (neat) 3325, 3024, 2932, 1754 cm^{-1}; HPLC (Alltech Econosphere 5μ, SiO_2, 96% Hex/IPA, 0.5 mL/min, obs at 234, 254, 265 nm) t_R = 10.8 min, 100%; HPLC (chiralpak-AD, 96% Hex/IPA, 0.5 mL/min, obs at 234, 254, 265 nm) t_R = 11.9, 13.0 min; 1:1 ratio at all three wavelengths; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 1 H), 7.20−7.23 (m, 3 H), 5.56 (s, 1 H), 3.72 (d, J = 11.3 Hz, 1 H), 3.56 (dd, J = 11.3, 2.2 Hz, 1 H), 2.92−2.97 (m, 1 H), 2.81−2.89 (m, 2 H), 2.15 (s, 3 H), 1.92−1.97 (m, 1 H), 1.4 (bs, 1 H), 1.34 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 145.5, 142.9, 128.2, 126.7, 124.6, 123.7, 98.3, 73.9, 64.3, 52.0, 40.2, 29.9, 27.5, 22.6, 21.1. HRMS (CI): found, m/z 275.1521 (M^+); $C_{16}H_{21}NO_3$ requires 275.1521.

Cis isomer: R_f 0.06 (20% EtOAc in hexane); mp = 98−101 °C; IR (KBr) 3309, 2930, 1735, 1245, 961 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.4 (m, 4 H), 5.75 (s, 1 H), 3.66 (dd, J = 11.4, 1.95 Hz, 1 H), 3.37 (d, J = 11.4 Hz, 1 H), 2.99 (ddd, J = 14.1, 9.3, 1.0 Hz, 1 H), 2.85−2.92 (m, 1 H), 2.78 (ddd, J = 12.5, 7.85, 1.5 Hz, 1 H), 2.19 (s, 3 H), 2.03−2.08 (m, 1 H), 1.6 (bs, 2 H, H_2O + OH), 1.41 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 145.7, 143.1, 128.3, 126.7, 124.8, 122.8, 93.2, 65.4, 63.3, 51.1, 39.8, 30.1, 27.6, 27.0, 21.2. HRMS (CI): found, m/z 275.1520 (M^+); $C_{16}H_{21}NO_3$ requires 275.1521. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.83; H, 7.44; N, 5.06.

3′,3′-Dimethyl-2′-thiophenylspiro[indan-1,3′-morpholine] (41). To a solution of racemic trans acetoxy acetal (257 mg, 1.10 mmol, 1.0 equiv) in 20 mL of CH_2Cl_2 were added TMSOTf (1.10 mL, 5.5 mmol, 5.0 equiv) and TMSSPh (2.1 mL, 11.0 mmol, 10.0 equiv). After being stirred for 3 days, the reaction was quenched with saturated $NaHCO_3$, extracted (3 × CH_2Cl_2), washed (15% NaOH, brine), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (flash, SiO_2, 7.5−20% EtOAc/hexanes) gave 25.1 mg (0.108 mmol, 10%) of starting acetal and 308 mg (0.946 mmol, 86%) of (±)-**41** as an inseparable 10:1 mixture of C2′ epimers: R_f 0.35 (20% EtOAc/hexanes); IR (neat) 3315, 2069, 2926, 1476, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) [major isomer] δ 7.5 (m, 3 H), 7.19−7.30 (m, 6 H), 5.27 (s, 1 H), 4.30 (dd, J = 11.4, 1.8 Hz, 1

H), 3.35 (d, J = 11.4 Hz, 1 H), 2.85−3.00 (m, 2 H), 2.80 (ddd, J = 12.4, 9.6, 2.0 Hz, 1 H), 2.05 (app q, J = 9.7 Hz, 1 H), 1.58 (m, 4 H), 1.35 (s, 3 H); ^{1}H NMR (500 MHz, $CDCl_3$) [minor isomer, characteristic peaks] δ 4.80 (s, 1 H), 3.81 (d, J = 11.2 Hz, 1 H), 3.41 (dd, J = 11.2, 1.9 Hz, 1 H), 1.52 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$,) δ 146.4, 142.8, 135.5, 131.3, 128.8, 128.2, 126.7 (2), 124.5, 123.7, 92.6, 64.8, 54.1, 53.5, 41.0, 30.0, 29.9, 29.8. Anal. Calcd for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30. Found: C, 74.01; H, 7.34; N, 4.27.

5′,5′-Dimethylspiro[indan-1,3′-morpholine] [(±)-42]. Racemic thioacetal **41** (46.0 mg, 0.141 mmol, 1.0 equiv) was dissolved in 5 mL of THF and cooled to −78 °C. Ammonia (ca. 10 mL) was condensed into the flask, and lithium metal (16 mg, 2.30 mmol, 16 equiv) was added to the solution. After the reaction mixture turned blue in color, it was allowed to proceed for an additional 2 min and quenched via dropwise addition of thioanisole (ca. 0.3 mL). The ammonia was allowed to evaporate, and the resulting residue was dissolved in water and Et_2O. The layers were separated, and the aqueous layer was extracted (3 × Et_2O). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (flash, SiO_2, 3−25% EtOAc/hexanes) gave 26.5 mg (0.122 mmol, 87%) of **42** as a white amorphous solid: R_f 0.12 (20% EtOAc in hexane); IR (neat) 3310, 3069, 2956, 1103, 1077 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.20 (m, 3H), 3.64 (d, J = 10.8 Hz, 1 H), 3.58 (d, J = 11.0 Hz, 1 H), 3.32 (dd, J = 10.8, 0.75 Hz, 1 H), 3.15 (dd, J = 11.0, 2.3 Hz, 1 H), 2.88 (m, 3 H), 1.90 (m, 1 H) 1.36 (m, 4 H), 1.06 (s, 1.36, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ *C* 146.8, 142.9, 64.7, 49.2; *C*H, 127.9, 126.4, 124.5, 123.8; *C*H_2, 77.4, 73.8, 40.2, 29.8; *C*H_3, 28.9, 27.6. Anal. Calcd for $C_{14}H_{18}NO_2$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.12; H, 7.99; N, 6.02.

5′,5′-Dimethylspiro[indan-1,3′-morpholine-*N*-oxyl] [(±)-43]. To a solution of racemic morpholine **42** (25.1 mg, 0.108 mmol, 1.0 equiv) in CH_2Cl_2 was added *m*-CPBA (37.3 mg, 0.215 mmol, 2.0 equiv) in one portion, and the resulting solution was allowed to stir for 6 h at room temperature. The reaction mixture was quenched with saturated K_2CO_3 solution, extracted (3 × CH_2Cl_2), washed (15% NaOH, brine), filtered, and concentrated under reduced pressure to give a red oil. Chromatography (flash, SiO_2, 5−10% EtOAc/hexanes) gave 24.6 mg (0.106 mmol, 98%) of racemic nitroxide **43** as a red oil which solidified upon standing to give a red glass: R_f 0.22 (20% EtOAc in hexane); IR (neat) 2971, 1469, 1300, 1102, 1061 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) broad unresolved peaks due to existence of paramagnetic radical; HPLC (normal phase analytical, 96% Hex/IPA, 0.5 mL/min, obs at 254 nm) t_R = 12.3 min, 100%; HPLC (chiralpak-AD, 98% Hex/IPA, 0.5 mL/min, obs at 234, 254, 265 nm) t_R = 17.0, 18.5 min; 1:1 ratio at all three wavelengths; HPLC (chiralpak-AD, 96% Hex/IPA, 0.5 mL/min, obs at 234, 254, 265 nm) t_R = 14.7, 15.8 min; 1:1 ratio at all three wavelengths. HRMS (CI): found, *m*/*z* 232.1344 (M^+); $C_{14}H_{18}NO_2$ requires 232.1337. Anal. Calcd for $C_{14}H_{18}NO_2$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.12; H, 7.99; N, 6.02.

Attempted Synthesis of Enantiomerically Pure Nitroxide 43. (5′*S*)-3′,3′-Dimethyl-2′-oxospiro[indan-1,5′-morpholine] [(+)-40] via Resolution with (+)-CSA. Morpholone **40** (32.4 mg, 0.140 mmol, 10% ee, 1.0 equiv) was dissolved in 20 mL of toluene. (+)-Camphorsulfonic acid was added, and the solution was refluxed for 12 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The resulting white solid was suspended in 20 mL of 3:1 pentane/EtOAc and brought to reflux. MeOH was added dropwise to the suspension until all of the solid dissolved. The solution was cooled to room temperature, then to 0 °C, and finally to −32 °C. After the solution was standing at −32 °C for 2 weeks, filtration gave 28 mg of crystalline white solid **40**·(+)CSA: mp 228−230 °C (dec); $[\alpha]^{24}_D$ = + 69.9° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (bs, 2 H), 7.85 (d, J = 7.6 Hz, 1 H), 7.16−7.35 (m, 3 H), 4.80 (d, J = 12.0 Hz, 1 H), 4.67 (d, J = 12.0 Hz, 1 H), 3.43 (m, 1 H), 2.83−2.95 (m, 3 H), 2.22−2.48 (m, 4 H), 1.77−1.98 (m, 10 H), 1.4 (app t, J = 9.6 Hz, 1 H), 1.27 (app t, J = 9.6 Hz, 1 H), 0.93 (s, 3 H), 0.70 (s, 3 H),

Salt **40**·(+)CSA was basified with saturated $NaHCO_3$ to give 14.1 mg (87%) of morpholone (+)-**40** in >99% ee as determined by chiral HPLC (Chiralpak AD, 96% Hex/IPA, 0.5 mL/min t_R = 17.1 (100%). The proton NMR of optically enriched (+)-**40** matched that of racemic **40** in all respects.

5′,5′-Dimethyl-4′-[((*R*)-1-phenylethyl)carbamoyl]spiro-[indan-1,3′-morpholine] (45). Racemic morpholine **42** (64 mg, 0.294 mmol) was dissolved in 2 mL of dry CH_2Cl_2, and to this solution was added (*R*)-(+)-α-methylbenzyl isocyanate (46 μL, 0.324 mmol, 1.1 equiv). After stirring of the solution for 12 h at room temperature, TLC analysis indicated incomplete reaction, so 2 mL of toluene was added and the mixture was refluxed for 3 h. The solvent was removed under reduced pressure, and the resulting yellow oil was purified by chromatography (flash, SiO_2, 20% EtOAc/hexanes) to give 105 mg (0.289 mmol, 98%) of a light yellow oil consisting of a 1:1 mixture of diastereomers. The diastereomers were separated using a 22 mm × 25 cm Alltech Econosphere 5μ SiO_2 Prep HPLC column, eluting with 1% IPA/hexane at 11 mL/min; 3.0 mg per 25 μL injection.

Early eluting diastereomer: R_f 0.19 (20% EtOAc/hexane), analytical HPLC (Alltech Econosphere, 5μ SiO_2, 4.6 mm × 25 cm, 98% Hex/IPA, 0.5 mL/min, obs at 254 nm) t_R = 9.2 min, 100%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.38 (m, 1 H), 7.31−7.33 (m, 2 H), 7.23−7.25 (m, 1 H), 7.14−7.21 (m, 3 H), 6.83 (dd, J = 6.85, 1.6 Hz, 2 H), 4.68 (dddd, J = 6.8, 6.8, 6.8, 6.8, 1 H), 4.51 (d, J = 6.8 Hz, 1 H), 3.58 (dd, J = 11.4, 1.5 Hz, 1 H), 3.48 (dd, J = 11.8, 1.35 Hz, 1 H), 3.47 (d, J = 11.4 Hz, 1 H), 3.44 (dd, 11.8, 2.50 Hz, 1 H), 2.79−2.89 (m, 2 H), 2.66 (ddd, J = 10.8, 6.65, 2.66 Hz, 1 H), 2.09 (dddd, J = 12.9, 10.0, 9.7, 2.7, 1 H), 1.53 (s, 3 H), 1.50 (s, 3 H), 0.91 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 145.0, 144.7, 142.0, 128.9, 128.3, 127.4, 126.7, 126.2, 125.6, 124.0, 79.8, 75.4, 68.5, 54.1, 49.7, 34.6, 29.2, 27.4, 23.2, 22.4. HRMS (CI, mixture): found, *m*/*z* 364.2151 (M^+); $C_{23}H_{28}N_2O_2$ requires 364.2151.

Late eluting diastereomer: R_f 0.19 (20% EtOAc/hexane), analytical HPLC (Alltech Econosphere, 5μ SiO_2, 4.6 mm × 25 cm, 98% Hex/IPA, 0.5 mL/min, obs at 254 nm) t_R = 10.1 min, 100%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.33 (m, 3 H), 7.28 (t, J = 3.6 Hz, 1 H), 7.23 (t, J = 6.7 Hz, 1 H), 7.13−7.19 (m, 2 H), 6.75 (d, J = 6.5 Hz, 2 H), 4.70 (dddd, J = 6.8, 6.7, 6.7, 6.7, 1 H), 4.63 (d, J = 6.8 Hz, 1 H), 3.60 (d, J = 11.8 Hz, 1 H), 3.47 (d, J = 11.4 Hz, 1 H), 3.38 (dd, J = 11.8, 2.3 Hz, 1 H), 3.13 (dd, J = 16.7, 9.9 Hz, 1 H), 2.86−3.90 (m, 1 H), 2.77−2.81 (m, 1 H), 2.35−2.42 (m, 1 H), 1.61 (s, 3 H), 1.47 (s, 3 H), 1.02 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 145.5, 144.6, 142.3, 129.4, 128.7(2), 126.8, 126.6, 125.9, 124.4, 80.4, 76.0, 69.0, 54.5, 50.2, 34.9, 29.8, 27.7, 23.6 (2).

(−)-5′,5′-Dimethylspiro[indan-1,3′-morpholine] [(−)-42] via Deprotection of Urea 46. To a solution of diastereomerically pure **46** (20 mg, 0.549 mmol, 1.0 equiv, > 95% de, ^{1}H NMR) in 2 mL of *n*BuOH was added 0.20 mL of a 25 wt % solution of NaOMe in MeOH (3.50 mmol, 6.3 equiv). The reaction mixture was sparged with argon for 15 min and refluxed for 8.5 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure (care must be taken as the product is somewhat volatile). The residue was diluted with H_2O and CH_2Cl_2 and the layers separated. The aqueous layer was extracted (3 × CH_2Cl_2), and the combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (flash, SiO_2, 20% EtOAc/hexanes) gave 11.6 mg (0.053 mmol, 97%) of (−)-**42** as a white amorphous solid: R_f 0.12 (20% EtOAc in hexane); $[\alpha]^{24}_D$ = − 69.6 ° (c = 1.16, CH_2Cl_2); IR (neat) 3310, 3069, 2956, 1103, 1077 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.20 (m, 3H), 3.64 (d, J = 10.8 Hz, 1 H), 3.58 (d, J = 11.0 Hz, 1 H), 3.32 (dd, J = 10.8, 0.75 Hz, 1 H), 3.15 (dd, J = 11.0, 2.3 Hz, 1 H), 2.88 (m, 3 H), 1.90 (m, 1 H) 1.36 (m, 4 H), 1.06 (s, 1.36). HRMS (CI): found, *m*/*z* 232.1344 (M^+); $C_{14}H_{18}NO_2$ requires 232.1337.

Deprotection of the late eluting urea gave amine (+)-**42** with identical properties with the exception of rotation: $[\alpha]^{24}_D$ = +82° (c = 1.0, CH_2Cl_2).

Oxidation of Optically Enriched Morpholine (+)-42 to (+)-43 under Buffered Conditions. To a solution of mor-

pholine (+)-**42** (5.6 mg, 0.0258 mmol, 1.0 equiv) in 4 mL of a 1:1 mixture of saturated $NaHCO_3$ and CH_2Cl_2 was added *m*-CPBA (8.9 mg, 0.0516 mmol, 2.0 equiv) in one portion. The resulting biphasic mixture was vigorously stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated 15% NaOH, extracted ($3 \times CH_2Cl_2$), washed (brine), filtered through cotton, and concentrated under reduced pressure to give 5.8 mg (0.0250 mmol, 97%) of (+)-**43** as a red oil, which was pure by TLC analysis: R_f 0.22 (20% EtOAc in hexane), HPLC (normal phase analytical, 96% Hex/IPA, 0.5 mL/min, obs at 234, 254, and 265 nm) $t_R = 12.3$ min, 100%; HPLC (chiralpak-AD, 98% Hex/IPA, 0.5 mL/min, obs at 234, 254, and 265 nm) $t_R = 17.2$, "18.5" min; 1:0 ratio at all three wavelengths.

Racemization Studies. Oxidation of Nitroxide (−)-43 with Bromine Followed by Concomitant Reduction with 2-Propanol and Saturated $NaHCO_3$. Nitroxide (−)-**43** (0.5 mg, 0.002 mmol, 1.0 equiv) was dissolved in 0.5 mL of CH_2Cl_2, and 20 μL of a 0.11 M solution of bromine (0.002 mmol, 2.0 equiv) in CH_2Cl_2 was added by microsyringe. The resulting bright orange solution was stirred for 2 min and quenched with a 1:1 mixture of IPA and saturated $NaHCO_3$. The suspension was diluted with 4 mL of CH_2Cl_2 and 4 mL of H_2O. The mixture was separated, and the aqueous phase was extracted ($3 \times CH_2Cl_2$). The combined organic layers were washed (brine), filtered through cotton, and concentrated under reduced pressure to give ca. 0.5 mg (0.002 mmol, 100%) of racemic **96** as a red oil, which was pure by TLC analysis: R_f 0.22 (20% EtOAc in hexane); HPLC (chiralpak-AD, 98% Hex/IPA, 0.5 mL/min, obs at 234, 254, and 265 nm) $t_R = 17.1$, 18.6 min; 1:1 ratio at all three wavelengths.

Acknowledgment. Support has been provided the National Science Foundation Presidential Young Investigator Program and the University of California, Irvine, CA. S.D.R. acknowledges Zeneca Inc. for support of his research program.

JO9808831