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An Improved Process for the Synthesis and Isolation of (*S*)-*N*-(1-Phenylethyl)hydroxylamine

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Abstract:

A three-step, single-solvent telescoped process amenable to the large-scale manufacture of (*S*)-*N*-(1-phenylethyl)hydroxylamine *p*-toluenesulfonic acid salt is reported. This synthetic protocol has been applied to the preparation of other chiral hydroxylamines.

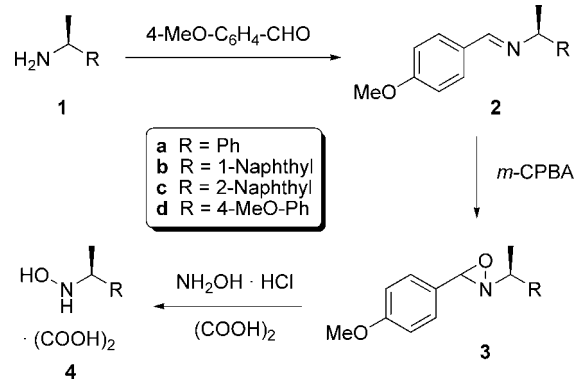
Introduction

The ability to access hydroxylamines continues to be important,[1] and the literature suggests several approaches to their synthesis. The most straightforward, in principle, is the partial oxidation of a primary amine, which has been best achieved using Oxone on a silica or alumina support[2] or with dimethyldioxirane.[3] The use of dibenzoyl peroxide has been reported for the oxidation of primary[4] and secondary[5] amines, although the reaction with primary amines also gives appreciable amounts of the *N*-benzoylated derivative. A complementary approach is the partial reduction of a nitro compound, such as the zinc-mediated reduction of 2-methyl-2-nitropropane.[6]

An alternative strategy, designed to overcome the limitation of over-reaction often encountered with more direct methods, is to carry out a stepwise process. For example, the oxidation of an imine to an oxaziridine may be carried out, whereupon acid-catalyzed hydrolysis, sometimes *via* isomerization to the nitrone, then affords a hydroxylamine.[7] A complication is that where the carbon substituent on the oxaziridine ring is an alkyl, rather than an aryl, group rearrangement to the amide product is preferred.[8] On the other hand, the oxidation of secondary amines to nitrones has been effected using hydrogen peroxide−urea complex in the presence of sodium tungstate.[9] These reactions have largely been performed on symmetrical amines where the regioselectivity of nitrone formation is not an issue, although more recently non-symmetrical nitrones have been prepared by this method.[10]

As part of our investigations into the synthesis of candidate drug molecules for the treatment of osteoarthritis, one promising strategy invoked the use of an enantiomerically pure chiral hydroxylamine, (*S*)-*N*-(1-phenylethyl)hydroxylamine. This material would be required in multikilogram quantities, but despite the interest in the synthesis of hydroxylamines, a viable, scalable process still seems to be absent from the literature.[11] The direct oxidation of a primary amine appears impractical on a large scale and is certainly not atom economical if it ultimately requires the use of Oxone.[12] The feasibility of the indirect methods to furnish such a hydroxylamine, or more likely a salt thereof, was thus explored, bearing in mind the necessity to ensure chiral integrity and chemical stability.

Scheme 1. **Oxaziridine route to hydroxylamines**



Wovkulich has previously published a method for the synthesis of our desired hydroxylamine and its isolation as the oxalic acid salt.[13] Starting from (*S*)-1-phenylethylamine (**1a**), *p*-anisaldimine (**2a**) was prepared and oxidized to oxaziridine (**3a**) with *m*-CPBA. Finally, cleavage with hydroxylamine hydrochloride before treatment with oxalic acid furnished the corresponding salt **4a** in 69% overall yield (Scheme 1). Presumably, salt formation protects the somewhat oxidation-sensitive free base and allows for the isolation of a stable solid.

Results and Discussion

We investigated this methodology and found that it worked smoothly in our hands. Extending the scope to other electronically neutral substrates, such as (*S*)-1-(naphthalen-1-yl)ethylamine (**1b**) and (*S*)-1-(naphthalen-2-yl)ethylamine (**1c**), gave the requisite hydroxylamine products in 53% and 47% yields, respectively. However, when an electron-rich substrate, (*S*)-1-

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(1) For a recent summary, see: Walz, A. J.; Möllmann, U.; Miller, M. J. *Org. Biomol. Chem.* **2007**, *5*, 1621.
(2) Fields, J. D.; Kropp, P. J. *J. Org. Chem.* **2000**, *65*, 5937.
(3) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1981.
(4) Milewska, M. J.; Chimiak, A. *Synthesis* **1990**, 233.
(5) Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537.
(6) Zhang, Y.; Xu, G. *Z. Naturforsch., B: Chem. Sci.* **1989**, *44*, 1475.
(7) For an early example, see: Połoński, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, *28*, 2453.
(8) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(9) Heydari, A.; Aslanzadeh, S. *Adv. Synth. Catal.* **2005**, *347*, 1223.
(10) Coşkun, N.; Parlar, A. *Synth. Commun.* **2005**, *35*, 2445.
(11) For the description of a large-scale preparation of a nitrone *via* the oxidation of a secondary amine with *m*-CPBA, see: Stappers, F.; Broeckx, R.; Leurs, S.; Van Den Bergh, L.; Agten, J.; Lambrechts, A.; Van den Heuvel, D.; De Smaele, D. *Org. Process. Res. Dev.* **2002**, *6*, 911. It is interesting to note that this oxidation presumably goes *via* the intermediacy of a hydroxylamine.
(12) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
(13) Wovkulich, P. M.; Uskokovič, M. R. *Tetrahedron* **1985**, *41*, 3455.

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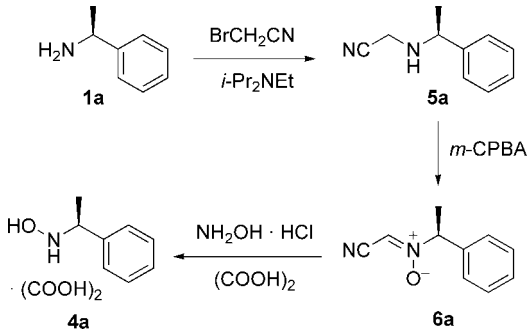
Scheme 2. **Nitrone route to hydroxylamines**



(4-methoxyphenyl)ethylamine (**1d**), was employed, the reaction sequence failed to afford the desired product, resulting instead in a number of unidentified degradants.

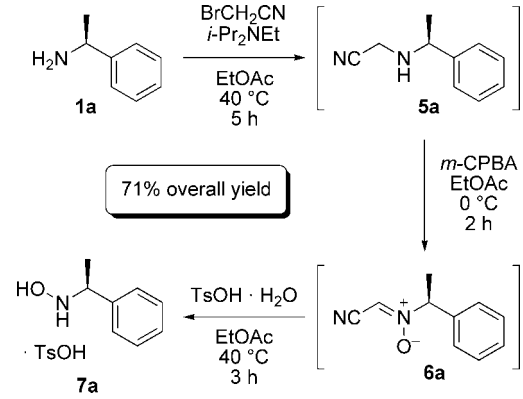
Later work by Fukuyama also described the synthesis of our desired compound (Scheme 2),[14,15] again starting from (*S*)-1-phenylethylamine (**1a**). Alkylation with bromoacetonitrile furnished secondary amine **5a**, to be used as the substrate for the oxidation step. Crucially, the nitrile group controlled the regioselectivity of the formation of nitrone **6a** and mitigated against racemization. Subsequent aminolysis using hydroxylamine hydrochloride at elevated temperatures was required to liberate the requisite chiral hydroxylamine, isolated again as the oxalic acid salt **4a**. Clearly, some of the problems evident from other syntheses were addressed in this approach, and we felt that it was a suitable starting point from which to develop a process for large-scale production. Certainly, starting a commercial manufacturing process with (*S*)-1-phenylethylamine would be highly attractive, it being readily available in bulk quantities at low cost and in high enantiomeric purity.

Nonetheless, to employ the Fukuyama procedure as such on scale presented several immediate concerns. Up to three isolations, four different solvents (including the use of both chloroform and methylene chloride), chromatography, and the heating of hydroxylamine hydrochloride were all issues that needed to be addressed.

Bretherick's states that explosions have occurred when heating hydroxylamine at atmospheric pressure and also when distilling mixtures of hydroxylamine hydrochloride and sodium hydroxide in methanol under reduced pressure.[16] Accordingly, the avoidance of heating hydroxylamine and its hydrochloride was considered paramount to the safe running of the process on scale.

Choosing a common solvent suitable for each of the individual steps would readily ameliorate the issue of multiple solvents. Such a solvent should be immiscible with water and stable to the reaction conditions. Three solvents that passed these criteria were immediately identified: methyl *tert*-butyl ether, ethyl acetate, and butyl acetate. Each of the steps worked in all three solvents, but the utilization of EtOAc gave the best results in terms of consistent conversion and ease of work-up. As a result, EtOAc became the solvent of choice (Scheme 3).

Scheme 3. **Optimized route to (*S*)-*N*-(1-phenylethyl)hydroxylamine**



The alkylation reaction was originally carried out in acetonitrile that was then evaporated *in vacuo* and the residue partitioned between saturated aq sodium bicarbonate, brine, and chloroform. Changing to EtOAc meant that an aqueous work-up could readily be performed without the need to swap solvents. Whilst the reaction could in fact be carried out in a biphasic mixture with saturated aq sodium bicarbonate, the losses to the aqueous phase were significant due to the water solubility of both the starting material and the secondary amine product **5a**. Incorporating just a small water wash of the EtOAc solution post-reaction in order to dissolve the precipitated Hünig's base hydrobromide proved effective in minimizing losses.

The oxidation step with *m*-CPBA was formerly carried out in methylene chloride. This has the advantage that the by-product *m*-chlorobenzoic acid, *m*-CBA, is completely insoluble in this solvent and can easily be removed by filtration. Changing the reaction solvent to EtOAc had the disadvantage of increased solubility of *m*-CBA. Consequently, *m*-CBA was therefore removed in our modified process by washing with saturated aq sodium bicarbonate. Using a stronger base, e.g. aq sodium hydroxide, resulted in coloration of the organic phase due to degradation of the intermediate nitrone **6a**. It was found to be imperative to remove all residual *m*-CBA as it interfered with the crystallization of the hydroxylamine salt in the final step. Any excess oxidant in the organic phase, as detected by starch/iodide paper, was also removed into the basic aqueous phase, which could then be treated with saturated aq sodium metabisulfite as required prior to disposal.

Moreover, *m*-CPBA had always been added portionwise as a solid to the reaction mixture, a procedure that would be laborious and operationally problematic on a large scale. Although the literature shows that methylene chloride is by far the most common solvent for *m*-CPBA oxidations, no doubt due to the ease of removal of *m*-CBA, the use of EtOAc is also precedented.[17] This facilitates the addition of an EtOAc solution of *m*-CPBA to an EtOAc solution of the secondary amine **5a** in order to effect the oxidation to the desired nitrone **6a**.

This oxidation step is rather energetic, measured at 469 kJ mol^{-1} in a Mettler Toledo RC1 calorimeter, which also indicated

(14) Amano, A.; Fukuyama, T.; Kuboyama, T.; Tokuyama, H.; Yamashita, T. *Synthesis* **2000**, 1299.

(15) Fukuyama, T.; Kuboyama, T.; Tokuyama, H. *Org. Synth.* **2003**, *80*, 207.

(16) Urben, P. G., Ed.; *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed; Butterworth-Heinemann: Oxford, UK, 1999; *Vol. 1*, pp 1662−1664.

(17) For an example of a process using *m*-CPBA in EtOAc for the oxidation of a sulfide to a sulfoxide, see: Milač, N. H.; Jereb, D. U.S. Patent 6,268,502, 2001.

no accumulation of the oxidant and that the reaction was dose controlled. Additional hazard testing showed that charging the entire *m*-CPBA solution to the reaction in one dose would result in an adiabatic temperature rise of ~170 °C. Adding the *m*-CPBA solution in four separate aliquots instead would give individual predicted temperature rises of 58 °C, 46 °C, 38 °C, and 32 °C, respectively, calculations which were supported by experimental data (first dose 55.5 °C, second dose 42.5 °C). With this degree of exothermicity, the reaction temperature could be kept below the boiling point of the solvent. This necessitated, however, some precautions on a larger scale to ensure that the feed vessel contained no more than a quarter of the total charge of *m*-CPBA in order to mitigate against dosing all of the oxidant solution to the reactor at once, either by accident or as a result of equipment failure.

It should be noted that *m*-CPBA is supplied at ~70% w/w strength, the remainder being *m*-CBA and water for stabilization. After effectively removing the water, the EtOAc solution of *m*-CPBA was investigated by DSC, which showed an exotherm onset at 105 °C. Invoking the 100 °C rule, the solution was added at 5 °C. This addition temperature was investigated further with an ARC measurement, which showed that the solution would be stable at 5 °C for several days.[18]

As indicated previously, an alternative procedure for the cleavage of nitrone **6a** was essential, as the heating of hydroxylamine hydrochloride to 60 °C was considered hazardous for a large-scale manufacture. One distinct advantage that hydroxylaminolysis did provide, however, was that the by-product NC−CH═NOH was water soluble and could thus easily be removed, albeit in a two-stage process. The reaction was performed in methanol and followed by a methylene chloride/water work-up. The methylene chloride solution of the sensitive free hydroxylamine was then evaporated *in vacuo* and the residue redissolved in methanol before precipitation of the desired product as the salt **4a** on addition of methanolic oxalic acid.

The continued use of EtOAc as the reaction solvent nicely obviated this rather convoluted end to the synthesis. Using *p*-toluenesulfonic acid monohydrate to function as both a catalyst for a formal hydrolysis through reaction of the adventitious water[19] in the EtOAc solution and then also to provide the counterion of the isolated salt made for an extremely expedient route to the requisite chiral hydroxylamine as the stable[20] *p*-toluenesulfonic acid salt **7a** in an overall strength-corrected yield of 71% for the three-step process (Scheme 3).

One issue that did require some attention was the disposal of the formal by-product from this modified hydrolytic cleavage of nitrone **6a**, namely formyl cyanide, since this presented the potential for the liberation of hydrogen cyanide. Dräger tube analysis of the headspace during the hydrolysis indicated up to 2.5 ppm of HCN was present during the reaction, diminishing to 0 ppm after 45 minutes. An adequate nitrogen sweep and suitable scrubbing of the exhaust gas was therefore imperative.

(18) For use of *m*-CPBA as a solution in EtOH and associated discussion, see: Prasad, J. S.; Vu, T.; Totleben, M. J.; Crispino, G. A.; Kacsur, D. J.; Swaminathan, S.; Thornton, J. E.; Fritz, A.; Singh, A. K. *Org. Process Res. Dev.* **2003**, *7*, 821.

(19) Bentley, P. H.; Brooks, G. *Tetrahedron Lett.* **1976**, *41*, 3735.

(20) Proton and carbon NMR analysis after 5 years storage at room temperature showed no discernable degradation.

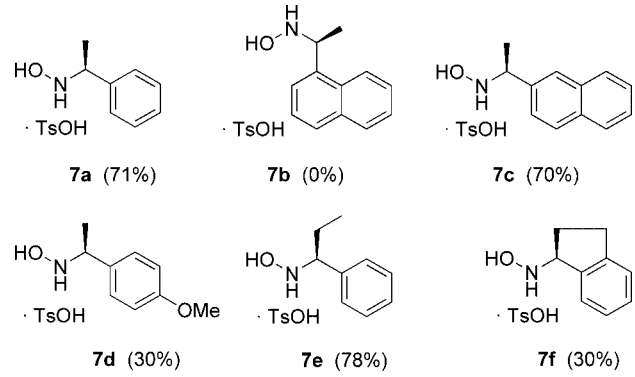


Figure 1. **Enantiomerically pure chiral hydroxylamines prepared using the telescoped process outlined herein (overall isolated yields in parentheses).**

In addition it was crucial that after isolation of the product by filtration, the mother liquor was treated with 2 M aq potassium carbonate to keep the pH above 9. This ensured that any cyanide was retained in the aqueous phase.

Confirmation of the preservation of stereochemical integrity throughout this synthetic sequence was attained through derivatisation of hydroxylamine **7a** to the *N*-benzoyl compound and analysis by chiral HPLC against a racemic standard, wherein >99% ee was always found. As expected, the nature of the counterion proved to have no bearing on the intended downstream use of this building block, and the *p*-toluenesulfonic acid salt performed as effectively as the oxalic acid salt in subsequent chemistry.

The synthetic procedure outlined above has been shown to be readily applicable to other chiral primary amine starting materials displaying a variety of steric and electronic characteristics, although the process conditions for the synthesis of the corresponding hydroxylamine derivatives have not been optimized (Figure 1).

Gratifyingly, where the oxaziridine approach had failed, (*S*)-1-(4-methoxyphenyl)ethylamine (**1d**) was successfully converted into the desired hydroxylamine salt **7d**. Conversely, whilst (*S*)-1-(naphthalen-1-yl)ethylamine (**1b**) had been converted to the corresponding hydroxylamine *via* the oxaziridine route, our process to the hydroxylamine *p*-toluenesulfonic acid salt (**7b**) failed. Interestingly, (*S*)-1-(naphthalen-2-yl)ethylamine (**1c**) could be transformed into the corresponding hydroxylamine salt **4c** or **7c** by either the oxaziridine or nitrone route, respectively. In contrast, modifying the α-alkyl substituent of the starting amine did not prove problematic, and smooth conversion to the expected hydroxylamine could be achieved, as exemplified by the ethyl analogue **7e** and the tethered indane derivative **7f**. Taken together these results suggest that the presence of an ortho substituent may present some limitation to this protocol. The steps to the intermediate nitrone were typically uneventful regardless of the aryl group, but the final hydrolysis failed in the case of **7b**, and the yield in the case of **7f** was low.

Conclusion

A scalable process for the synthesis of (*S*)-*N*-(1-phenylethyl)hydroxylamine from readily available (*S*)-α-methylbenzylamine and its isolation as the stable *p*-toluenesulfonic acid salt

7a has been developed by judicious selection of solvent, reagents and conditions. Anhydrous conditions were not required and allowed the use of reagent grade solvent throughout. The process has been proven in a large-scale laboratory manufacturing campaign, where the potential hazards were managed in a controlled manner, to deliver 4.5 kg of material in excellent quality.[21] Furthermore, this synthetic method has been shown to have applicability to the preparation of other chiral hydroxylamines.

Experimental Section

All reagents and solvents were used without further purification or drying. Solutions of *m*-CPBA in EtOAc were made without heating to aid dissolution and used immediately. Any unused *m*-CPBA solution was treated with saturated aq sodium metabisulfite solution before disposal. NMR spectra were obtained in $CDCl_3$, CD_3OD, or DMSO-d_6 on a Varian Inova 400 MHz spectrometer. All ^1H spectra are relative to the TMS signal and ^{13}C spectra to the relevant solvent peak. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR. Mass spectroscopy was performed on a Waters Micromass GCT.

(*S*)-2-(1-Phenylethylamino)acetonitrile (5a). (*S*)-α-Methylbenzylamine (50 mL, 0.39 mol) and Hünig's base (75.8 mL, 0.43 mol) were dissolved in ethyl acetate (250 mL), and the solution was heated to 40 °C. Bromoacetonitrile (30.6 mL, 0.43 mol) was added over 2 h. At the end of the addition, an ethyl acetate (25 mL) line wash was added, whereupon the reaction mixture was stirred for an additional 3 h. The suspension was then cooled to 20 °C and washed with water (75 mL) to afford an ethyl acetate solution of **5a**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, $J = 6.7$ Hz, 3H), 3.24 (d, $J = 17.4$ Hz, 1H), 3.54 (d, $J = 17.4$ Hz, 1H), 4.01 (q, $J = 6.5$ Hz, 1H), 7.25−7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 35.0, 56.8, 117.8, 126.9, 127.7, 128.7, 142.9.

(*S*)-*N*-(Cyanomethylene)-1-phenylethylamine Oxide (6a). The ethyl acetate solution of **5a** was cooled to 0 °C, and a freshly prepared solution of *m*-CPBA (210.4 g, 0.85 mol) in ethyl acetate (250 mL) was added, keeping the internal temperature below 5 °C, typically over 2 h. At the end of the addition, an ethyl acetate (50 mL) line wash was added and the temperature increased to 20 °C. The reaction mixture was washed with saturated aq sodium bicarbonate (3 × 250 mL) and brine (250 mL) to afford an ethyl acetate solution of **6a**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (d, $J = 6.9$ Hz, 3H), 5.20 (q, $J = 6.8$ Hz, 1H), 6.73 (s, 1H), 7.37−7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 76.3, 112.2, 127.3, 128.9, 129.2, 129.7, 136.2.

(*S*)-*N*-(1-Phenylethyl)hydroxylamine *p*-Toluenesulfonic Acid Salt (7a). The ethyl acetate solution of **6a** was heated to 40 °C, *p*-toluenesulfonic acid monohydrate (74.5 g, 0.39 mol) and further ethyl acetate (50 mL) were added, and the reaction mixture was stirred for 3 h [CAUTION: Potential release of HCN in headspace; ensure adequate ventilation!]. Seed was added, if required, at the end of the hold period, and the reaction mixture was ramp cooled to 0 °C over 3 h. The hydroxylamine salt was isolated by filtration and washed with EtOAc (50 ml) to leave the product as a colorless solid. The product was dried *in vacuo* at 40 °C (85.6 g, 71% overall yield). Mp 126−128 °C. FT-IR 2838, 1161, 1033, 1006 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 1.66 (d, $J = 6.9$ Hz, 3H), 2.35 (s, 3H), 4.50 (q, $J = 6.9$ Hz, 1H), 7.22 (d, $J = 7.9$ Hz, 2H), 7.41−7.48 (m, 5H), 7.69 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 16.1, 21.4, 63.0, 127.0, 129.5, 129.9, 130.3, 131.0, 135.7, 141.8, 143.4. HRMS (CI-TOF) *m/z* $[M + H]^+$ calcd for $C_8H_{12}NO$ 138.0919, found 138.0859. Enantioselectivity was determined after conversion to the corresponding *N*-benzoylhydroxylamine and found to be >99% ee by chiral HPLC (DAICEL CHIRALPAK AS, 25 cm × 4.6 mm, isopropanol/hexane 40:60, 1.0 mL/min, 30 °C, λ 254 nm, t_R 9.18 min [*R*], 18.22 min [*S*]).

The following compounds were synthesized using the appropriate procedure as described above for compounds **5a**, **6a**, and **7a**.

(*S*)-2-[1-(Naphthalen-1-yl)ethylamino]acetonitrile (5b): ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, $J = 6.7$ Hz, 3H), 1.73 (s, 1H), 3.32 (d, $J = 17.7$ Hz, 1H), 3.57 (d, $J = 17.7$ Hz, 1H), 4.84 (q, $J = 6.5$ Hz, 1H), 7.42−7.53 (m, 3H), 7.62 (d, $J = 6.9$ Hz, 1H), 7.75 (d, $J = 8.2$ Hz, 1H), 7.85 (d, $J = 7.9$ Hz, 1H), 8.27 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 35.2, 53.0, 118.1, 122.9, 123.5, 125.6, 125.7, 126.1, 128.0, 129.0, 131.2, 134.1, 138.4.

(*S*)-*N*-(Cyanomethylene)-1-(naphthalen-1-yl)ethylamine oxide (6b): ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (d, $J = 6.9$ Hz, 3H), 5.92 (q, $J = 6.9$ Hz, 1H), 6.47 (s, 1H), 7.49−7.61 (m, 3H), 7.69 (d, $J = 7.2$ Hz, 1H), 7.89−7.93 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 73.5, 106.5, 112.4, 121.9, 125.3, 126.6, 127.8, 129.4, 130.1, 130.9, 133.7, 133.9, 129.8.

(*S*)-2-[1-(Naphthalen-2-yl)ethylamino]acetonitrile (5c): ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, $J = 6.7$ Hz, 3H), 1.71 (s, 1H), 3.20 (d, $J = 17.4$ Hz, 1H), 3.51 (d, $J = 17.7$ Hz, 1H), 4.15 (q, $J = 6.5$ Hz, 1H), 7.42−7.48 (m, 3H), 7.77−7.83 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 35.1, 56.9, 117.9, 124.6, 125.9, 126.1, 126.3, 127.7, 127.8, 128.7, 133.2, 133.4, 140.3.

(*S*)-*N*-(Cyanomethylene)-1-(naphthalen-2-yl)ethylamine oxide (6c): ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (d, $J = 6.9$ Hz, 3H), 5.34 (q, $J = 6.8$ Hz, 1H), 6.78 (s, 1H), 7.46−7.53 (m, 3H), 7.82−7.87 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 76.5, 106.3, 112.4, 124.2, 126.9, 127.1, 127.2, 127.8, 128.2, 129.2, 133.0, 133.6 (2C).

(*S*)-2-[1-(Naphthalen-2-yl)ethyl]hydroxylamine *p*-toluenesulfonic acid salt (7c): mp 137−138 °C. FT-IR 2804, 1196, 1159, 1123, 1035, 1010 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 1.76 (d, $J = 6.9$ Hz, 3H), 2.32 (s, 3H), 4.71 (q, $J = 6.9$ Hz, 1H), 7.18 (d, $J = 7.9$ Hz, 2H), 7.50−7.58 (m, 3H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.86−7.94 (m, 3H), 8.00 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 21.3, 63.0, 126.0, 126.9, 127.8, 128.2, 128.7, 129.3, 129.4, 129.8, 130.1, 132.8,134.5, 135.1, 141.8, 143.3. HRMS (CI-TOF) *m/z* $[M + H]^+$ calcd for $C_{12}H_{14}NO$ 188.1075, found 188.1067.

(*S*)-2-[1-(4-Methoxyphenyl)ethylamino]acetonitrile (5d): mp 64−65 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, $J = 6.4$ Hz, 3H), 3.24 (d, $J = 17.7$ Hz, 1H), 3.54 (d, $J = 17.4$ Hz, 1H), 3.80 (s, 3H), 3.98 (q, $J = 6.5$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz,

(21) Patel, I.; Smith, N.; Tyler, S. N. G. PCT Int. Appl. WO 2008/029090, 2008.

2H), 7.26 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 34.9, 55.3, 56.1, 114.1, 117.8, 128.0, 134.8, 159.1.

(*S*)-*N*-(Cyanomethylene)-1-(4-methoxyphenyl)ethylamine oxide (6d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (d, J = 6.9 Hz, 3H), 3.81 (s, 3H), 5.17 (q, J = 6.9 Hz, 1H), 6.76 (s, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 55.4, 63.2, 105.8, 112.5, 114.2, 114.5, 128.1, 129.0.

(*S*)-*N*-[1-(4-Methoxyphenyl)ethyl]hydroxylamine *p*-toluenesulfonic acid salt (7d): mp 139−141 °C. FT-IR 2710, 1183, 1031, 1005 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50 (d, J = 6.7 Hz, 3H), 2.27 (s, 3H), 3.74 (s, 3H), 4.42 (q, J = 6.8 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 10.73 (br s, 1H), 11.22 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.9, 20.8, 55.2, 59.8, 114.0, 125.5, 126.8, 128.2, 129.8, 138.0, 145.1, 159.8. HRMS (CI-TOF) m/z [M + H]$^+$ calcd for $C_9H_{14}NO_2$ 168.1025, found 168.0977.

(*S*)-2-(1-Phenylpropylamino)acetonitrile (5e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 1.79−1.62 (m, 3H), 3.20 (d, J = 17.7 Hz, 1H), 3.54 (d, J = 17.7 Hz, 1H), 3.74 (dd, J = 7.7, 6.2 Hz, 1H), 7.36−7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 30.7, 35.0, 63.4, 117.9, 127.6 (2C), 127.7, 128.6 (2C), 141.2.

(*S*)-*N*-(Cyanomethylene)-1-phenylpropylamine oxide (6e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 2.07−1.96 (m, 1H), 2.46−2.35 (m, 1H), 4.93 (dd, J = 8.5, 6.4 Hz, 1H), 6.92 (s, 1H), 7.39−7.36 (m, 3H), 7.45−7.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 26.2, 82.6, 106.4, 112.4, 127.6, 129.0, 129.6, 135.5.

(*S*)-*N*-(1-Phenylpropyl)hydroxylamine *p*-toluenesulfonic acid salt (7e): mp = 166 °C. FT-IR 2845, 1161, 1126, 1034, 1005 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 (t, J = 7.7 Hz, 3H), 2.03−1.92 (m, 1H), 2.28−2.18 (m, 1H), 2.35 (s, 3H), 4.25 (dd, J = 11.0, 4.6 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.46−7.42 (m, 5H), 7.72 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.1, 20.2, 22.6, 67.8, 125.8, 128.7, 128.8, 129.1, 129.8, 132.8, 140.7, 142.2. HRMS (CI-TOF) m/z [M + H]$^+$ calcd for $C_9H_{14}NO$ 152.1075, found 152.1055.

(*S*)-2-(2,3-Dihydro-1*H*-inden-1-ylamino)acetonitrile (5f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 1H), 1.80−1.88 (m, 1H), 2.37−2.46 (m, 1H), 2.78−2.86 (m, 1H), 2.99−3.06 (m, 1H), 3.60 (s, 2H), 4.36 (t, J = 6.0 Hz, 1H), 7.17−7.26 (m, 3H), 7.30 (d, J = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 33.2, 35.2, 62.3, 118.5, 124.1, 125.0, 126.5, 128.1, 143.4, 143.8.

(*S*)-*N*-(Cyanomethylene)-2,3-dihydro-1*H*-inden-1-amine oxide (6f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50−2.60 (m, 2H), 2.92−2.99 (m, 1H), 3.15−3.23 (m, 1H), 5.48−5.51 (m, 1H), 6.65 (s, 1H), 7.26−7.42 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 31.5, 81.9, 106.0, 112.4, 125.2, 125.7, 127.5, 130.5, 136.7, 145.9.

(*S*)-*N*-(2,3-Dihydro-1*H*-inden-1-yl)hydroxylamine *p*-toluenesulfonic acid salt (7f): mp 137−139 °C. FT-IR 2983, 1123, 1034 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.18−2.25 (m, 1H), 2.27 (s, 3H), 2.33−2.43 (m, 1H), 2.83−2.90 (m, 1H), 3.03−3.11 (m, 1H), 4.85−4.88 (m, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.24−7.38 (m, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.7 Hz, 1H), 10.88 (br s, 1H), 11.36 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 26.1, 29.9, 52.9, 125.0, 125.5, 126.4, 126.6, 128.2, 129.8, 135.3, 138.0, 145.1, 145.5. HRMS (CI-TOF) m/z [M + H]$^+$ calcd for $C_9H_{12}NO$ 150.0919, found 150.0869.

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Supporting Information Available

^{1}H, ^{1}H−^{1}H COSY, and ^{13}C NMR spectra for compounds **5a**−**f**, **6a**−**f**, and **7a**,**c**−**f**; IR spectra for compounds **7a**,**c**−**f**; MS data for compounds **7a**,**c**−**f**; chiral HPLC chromatograms for **7a**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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