# Enantioselective Thiourea-Catalyzed Intramolecular Cope-Type Hydroamination

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## Supporting Information

## 1. General Information

**General Procedure.** Unless otherwise noted, all reactions were performed in flame-dried round-bottom flasks sealed with a rubber septum under a nitrogen atmosphere. Air and moisture sensitive liquids were transferred using stainless steel cannulae or syringes. Flash chromatography was performed using silica gel ZEOprep60 ECO 40-63 micron from American International Chemical, Inc.

**Materials.** Commercial reagents were purchased from VWR, Acros, and Sigma-Aldrich and used as received with the following exceptions: dichloromethane and tetrahydrofuran were dried by passing through columns of activated alumina. Acetonitrile was dried by passing through a column of activated molecular sieves. Triethylamine and *N*,*N*-diisopropylethylamine were distilled from $CaH_2$ at 760 torr.

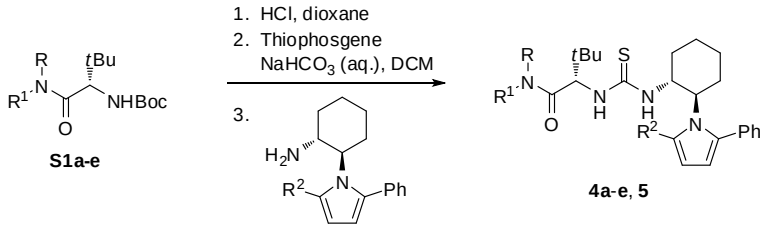
**Instrumentation.** Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Varian Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$: δ7.27). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants in Hertz (Hz). Mass spectroscopic (MS) data were obtained using an Agilent 6120 Single Quadrupole LC/MS instrument equipped with an ESI-APCI multimode source. Infrared (IR) spectra were obtained using a Bruker Tensor 27 FTIR spectrophotometer. Data are represented as follows: frequency of absorption (cm–1), intensity of absorption (s = strong, m = medium, w = weak). Optical rotation data were obtained using a 1 mL cell with a 0.5 dm path length on a Jasco P-2000 polarimeter. Chiral HPLC analysis was performed using Agilent 1200 series instruments.

**Abbreviations used:** ee = enantiomeric excess, HPLC = high performance liquid chromatography, $Et_3N$ = triethylamine, AcOH = acetic acid, DCM = dichloromethane, HCl = hydrogen chloride, $NaHCO_3$ = sodium bicarbonate, Boc = *tert*-butoxycarbonyl, LiCl = lithium chloride, $Et_3B$ = triethylborane, $HONH_3Cl$ = hydroxylamine hydrochloride, NaOAc = sodium acetate, MeOH = methanol, $NaCNBH_3$ = sodium cyanoborohydride, $Boc_2O$ = di-*tert*-butyl dicarbonate, TFA = trifluoroacetic acid, $Pd(OAc)_2$ = palladium acetate, $PPh_3$ = triphenylphosphine, $(MeO)_3CCH_3$ = trimethyl orthoacetate, DIBAL-H = diisobutylaluminum hydride, DIPEA = *N*,*N*-diisopropylethylamine, *n*BuLi = *n*-butyllithium and THF = tetrahydrofuran.

## 2. Catalyst Preparation and Characterization Data

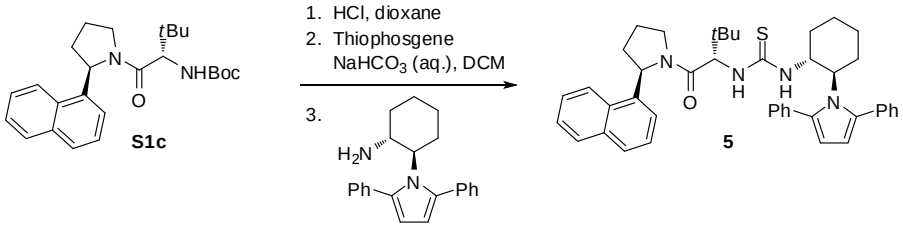
Catalysts **3a-e** were synthesized via previously reported methods. The spectral data matched those reported in the literature.[1]

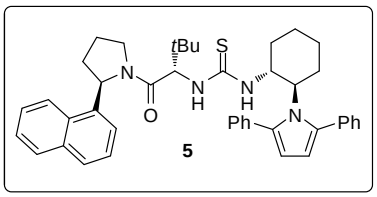
**General synthetic route for the preparation of catalysts 4a-e, 5**




Intermediates **S1a-e** were synthesized via previously reported methods. The spectral data matched those reported in the literature.[1] 2-pyrrolylcyclohexylamines were synthesized via previously reported methods. The spectral data matched those reported in the literature.[2]

**Syntheis of optimal catalyst 5**



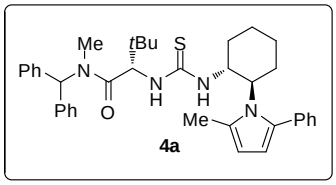

**1-((*S*)-3,3-dimethyl-1-((*R*)-2-(naphthalen-1-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)-3-((1*R*,2*R*)-2-(2,5-diphenyl-1*H*-pyrrol-1-yl)cyclohexyl)thiourea (5):** To Boc-protected amine **S1c** (640 mg, 1.56 mmol) was added excess hydrogen chloride (7.8 mL, 4M in dioxane) and the mixture was stirred for 1 h at 23 ºC. The mixture was concentrated to yield the crude hydrochloride salt. Dichloromethane (12 mL) and saturated aqueous sodium bicarbonate (12 mL) were added to the crude salt, and the mixture was cooled to 0 ºC. Thiophosgene (0.130 mL, 1.7 mmol) was added to the organic (lower) phase of the mixture by syringe, and the mixture was stirred at 0 ºC for 30 minutes. Dichloromethane (20 mL) was added, and organic portion was separated. The aqueous was extracted with dichloromethane (2 x 20 mL) and the combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The crude isothiocyanate was dissolved in dichloromethane (5 mL) and the pyrrolylcyclohexylamine (642 mg, 2.03 mmol) was added as a solution in dichloromethane (5 mL). The mixture was stirred at 23 ºC for 14 h, then concentrated *in vacuo*, and purified by flash chromatography on silica gel to yield the desired

[1] For catalyst **3a** see: (a) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968. For catalyst **3b** see: (b) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. For catalyst **3c-e** see: (c) Knowles, R. R.; Lin, S.: Jacobsen, E. N. *J. Am. Chem. Soc.* 2010, 132, 5030.

[2] (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558 (b) Jones, C. R.; Pantos, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 7391.

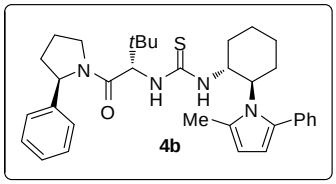
product **5** (755 mg, 72% yield). $[\alpha]_D^{23} = -10.2^o$ (c=1.0, $CHCl_3$). The compound exists as a 2.5:1 mixture of amide rotamers in $CDCl_3$. $^1H$ NMR (500MHz ,$CDCl_3$) major rotamer resonances δ = 7.98 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H), 7.65 - 7.34 (m, 13 H), 7.24 - 7.19 (m, 1 H), 7.02 (d, *J* = 6.9 Hz, 1 H), 6.19 (br. s., 2 H), 5.88 (d, *J* = 7.8 Hz, 1 H), 5.70 (d, *J* = 9.6 Hz, 1 H), 5.53 (d, *J* = 9.6 Hz, 1 H), 5.34 (br. s., 1 H), 4.62 - 4.49 (m, 1 H), 4.04 - 3.94 (m, 1 H), 3.89 - 3.72 (m, 1 H), 3.58 - 3.41 (m, 1 H), 2.49 - 2.31 (m, 1 H), 2.27 - 2.10 (m, 1 H), 2.03 - 1.23 (m, 10 H), 1.13 (s, 9 H); selected minor rotamer resonances: δ = 8.29 (d, *J* = 8.2 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 6.30 (br. s, 1 H), 5.64 (d, *J* = 9.6 Hz, 1 H), 5.12 (br. s, 1 H), 5.02 (d, *J* = 10.1 Hz, 1 H), 4.16 - 4.05 (m, 1 H), 0.72 (s, 9 H); $^{13}C$ NMR (126MHz ,$CDCl_3$) major and minor rotamer resonances δ = 181.6, 181.4, 181.4, 172.0, 169.8, 138.4, 136.7, 134.0, 133.8, 131.4, 130.0, 128.7, 128.6, 127.8, 127.0, 126.3, 125.8, 125.7, 125.2, 124.5, 124.0, 123.9, 123.2, 121.6, 112.7, 109.8, 62.8, 62.0, 61.0, 60.7, 59.1, 58.1, 57.3, 56.3, 48.5, 47.3, 35.6, 34.9, 34.6, 34.0, 33.8, 33.5, 33.2, 32.9, 32.8, 29.0, 26.7, 26.6, 25.9, 25.7, 25.3, 24.1, 23.9, 23.4, 22.6, 21.4, 20.7 (the carbon resonances for the 2,5-aryl groups of the pyrrole are broadened and difficult to assign); FTIR: 3372 (w), 3256 (w), 3069 (w), 2953 (m), 2868 (m), 1638 (s), 1610 (s), 1506 (s), 1443 (s), 1308 (m); LRMS $[M+Na]^+$ calculated for $C_{43}H_{48}N_4NaOS$: 691.34, found: 691.2

**Characterization data for all novel catalysts in Table 1**



**4a**

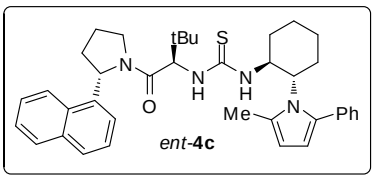
**(*S*)-*N*-benzhydryl-*N*,3,3-trimethyl-2-(3-((1*R*,2*R*)-2-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)thioureido)butanamide (4a):** $[\alpha]_D^{23} = -16.0^o$ (c=1.0, $CHCl_3$); $^1H$ NMR (500MHz ,$CDCl_3$) δ = 7.55 - 7.04 (m, 15 H), 6.09 - 5.98 (m, 2 H), 5.85 (br. s., 1 H), 5.49 (d, *J* = 9.2 Hz, 1 H), 5.23 (br. s., 1 H), 4.47 (br. s, 1 H), 4.16 - 3.93 (m, 2 H), 3.04 (s, 3 H), 2.49 (br. s., 3 H), 1.89 (m, 2 H), 1.81 - 1.65 (m, 2 H), 1.52 - 1.19 (m, 4 H), 0.97 (s, 9 H); $^{13}C$ NMR (126MHz ,$CDCl_3$) δ = 182.1, 172.7, 139.2, 138.1, 136.0, 134.2, 129.8, 129.4, 128.7, 128.5, 128.4, 128.1, 127.6, 127.1, 127.0, 110.2, 108.7, 60.9, 60.4, 59.8, 56.1, 36.1, 33.7, 33.2, 32.3, 26.6, 25.7, 24.6, 15.3; FTIR: 3358 (m), 3292 (m), 3062 (m), 3030 (m), 2939 (s), 2861 (m), 1631 (s), 1522 (s), 1446 (m), 1408 (m), 1366 (m); LRMS $[M+Na]^+$ calculated for $C_{38}H_{46}N_4NaOS$: 629.33, found: 629.3



**4b**

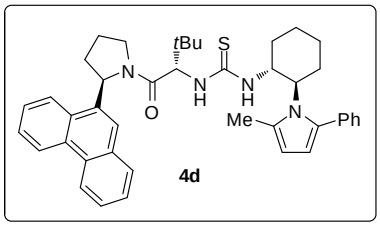
**1-((*S*)-3,3-dimethyl-1-oxo-1-((*R*)-2-phenylpyrrolidin-1-yl)butan-2-yl)-3-((1*R*,2*R*)-2-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)thiourea (4b):** $[\alpha]_D^{24} = 19.8^o$ (c=1.0, $CHCl_3$); The compound exists as a 1.25:1 mixture of amide rotamers in $CDCl_3$. $^1H$ NMR (500MHz ,$CDCl_3$) major rotamer resonances δ = 7.49 - 7.05 (m, 10 H), 5.94 - 5.80 (m, 3 H), 5.40 (d, *J* = 9.2 Hz, 1 H), 5.22 (br. s., 1 H), 5.14 (d, *J* = 7.8 Hz, 1 H), 4.70 - 4.51 (m, 1 H), 4.37 (t, *J* = 8.0 Hz, 1 H), 3.84 - 3.62 (m, 2 H), 2.47 (br. s., 3 H), 2.37 - 1.58 (m, 12 H), 1.08 - 0.99 (m, 9 H); $^{13}C$ NMR (126MHz ,$CDCl_3$) major and minor rotamer resonances δ = 181.8, 171.8, 169.9, 144.2, 142.4, 136.0, 134.3, 134.1, 129.6, 129.5, 129.1, 128.8, 128.6, 128.4, 128.3, 127.2, 127.0, 126.9, 126.7, 126.4, 125.3, 110.3, 109.9, 108.8, 108.6, 62.3, 61.2, 60.8, 60.1, 59.7, 56.1, 55.9, 48.4, 47.0, 35.7, 35.4, 35.3, 34.2, 33.7, 32.3, 32.1, 29.7, 29.0, 26.5, 26.4, 25.7, 25.6, 24.6, 24.5, 23.1, 21.9, 15.6, 15.4; FTIR: 3385 (m), 3066 (w),

2948 (m), 2870 (m), 1635 (s), 1518 (s), 1436 (s); LRMS $[M+Na]^+$ calculated for $C_{34}H_{44}N_4NaOS$: 579.31, found: 579.2



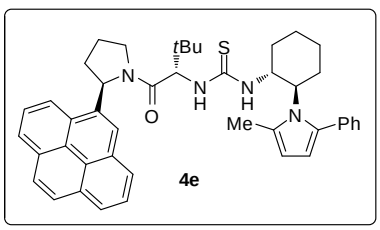
*ent*-**4c**

**1-((*R*)-3,3-dimethyl-1-((*S*)-2-(naphthalen-1-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)-3-((1*S*,2*S*)-2-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)thiourea (*ent*-4c)**: $[\alpha]_D^{24} = -15.2^o$ (c=1.0, $CHCl_3$); The compound exists as a 2.5:1 mixture of amide rotamers in $CDCl_3$. $^1H$ NMR (500MHz ,$CDCl_3$) major rotamer resonances δ = 8.00 (d, *J* = 8.2 Hz, 1 H), 7.85 (d, *J* = 8.7 Hz, 1 H), 7.63 - 7.28 (m, 8 H), 7.08 (d, *J* = 6.9 Hz, 1 H), 6.02 (br. s., 1 H), 5.96 - 5.89 (m, 2 H), 5.49 (d, *J* = 9.2 Hz, 1 H), 5.30 (br. s., 1 H), 4.56 (br. s., 1 H), 4.35 - 4.19 (m, 1 H), 4.00 (br. s., 1 H), 3.87 - 3.77 (m, 1 H), 3.76 - 3.65 (m, 1 H), 2.50 (br. s., 3 H), 2.42 - 1.79 (m, 10 H), 1.01 (s, 9 H); $^{13}C$ NMR (126MHz ,$CDCl_3$) major and minor rotamer resonances δ = 181.8, 171.9, 170.0, 138.3, 136.7, 136.0, 134.1, 133.8, 133.1, 130.1, 130.0, 129.6, 129.5, 128.9, 128.8, 128.6, 128.5, 128.5, 128.0, 127.8, 127.1, 126.2, 125.8, 125.7, 125.3, 125.3, 124.5, 124.1, 123.8, 123.3, 121.7, 110.4, 109.9, 108.7, 108.7, 62.5, 61.5, 60.4, 60.1, 59.7, 59.0, 58.2, 56.2, 56.0, 48.5, 47.1, 37.0, 35.7, 35.3, 33.9, 33.7, 33.7, 32.8, 32.4, 32.2, 26.7, 26.5, 25.7, 25.6, 24.7, 24.5, 23.3, 21.5; FTIR: 3340 (m), 3275 (m), 3055 (w), 2934 (m), 2866 (m), 1640 (m), 1607 (s), 1512 (s), 1445 (s), 1363 (m), 1311 (s); LRMS $[M+Na]^+$ calculated for $C_{38}H_{46}N_4NaOS$: 629.33, found: 629.2



**4d**

**1-((*S*)-3,3-dimethyl-1-oxo-1-((*R*)-2-(phenanthren-9-yl)pyrrolidin-1-yl)butan-2-yl)-3-((1*R*,2*R*)-2-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)thiourea (4d):** $[\alpha]_D^{25} = 59.1^o$ (c=0.45, $CHCl_3$); The compound exists as a 1.6:1 mixture of amide rotamers in $CDCl_3$. $^1H$ NMR (500MHz ,$CDCl_3$) major rotamer resonances δ = 8.72 (d, *J* = 7.8 Hz, 1 H), 8.61 (d, *J* = 8.7 Hz, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 7.90 (d, *J* = 7.3 Hz, 1 H), 7.73 - 7.29 (m, 10 H), 6.14 - 5.88 (m, 3 H), 5.82 (br. s., 1 H), 5.56 (br. s., 1 H), 5.47 (d, *J* = 9.6 Hz, 1 H), 4.73 (d, *J* = 10.5 Hz, 1 H), 3.94 (br. s., 1 H), 3.90 - 3.80 (m, 1 H), 3.72 (d, *J* = 16.9 Hz, 1 H), 2.34 (s, 3 H), 2.21 - 1.61 (m, 12 H), 1.10 (s, 9 H); $^{13}C$ NMR (126MHz ,$CDCl_3$) major and minor resonances δ = 182.0, 182.0, 172.1, 170.2, 136.2, 136.1, 134.2, 131.5, 131.3, 131.0, 130.8, 130.7, 130.3, 130.0, 129.8, 129.6, 129.2, 129.2, 129.0, 128.9, 128.5, 128.4, 127.3, 127.1, 126.7, 126.7, 126.5, 126.4, 126.1, 126.0, 125.0, 124.5, 123.9, 123.3, 123.0, 122.9, 122.4, 122.2, 122.1, 110.4, 109.8, 108.6, 66.7, 63.2, 61.5, 60.1, 59.7, 59.3, 58.4, 56.2, 55.8, 48.4, 47.1, 35.5, 35.2, 33.7, 33.5, 32.2, 26.8, 26.6, 26.5, 25.7, 25.4, 24.7, 24.3, 23.3, 21.6, 15.6, 15.4; FTIR: 3395 (m), 3155 (w), 3074 (m), 2947 (m), 2871 (m), 1638 (s), 1525 (s), 1435 (m); LRMS $[M+Na]^+$ calculated for $C_{42}H_{48}N_4NaOS$: 679.34, found: 679.3



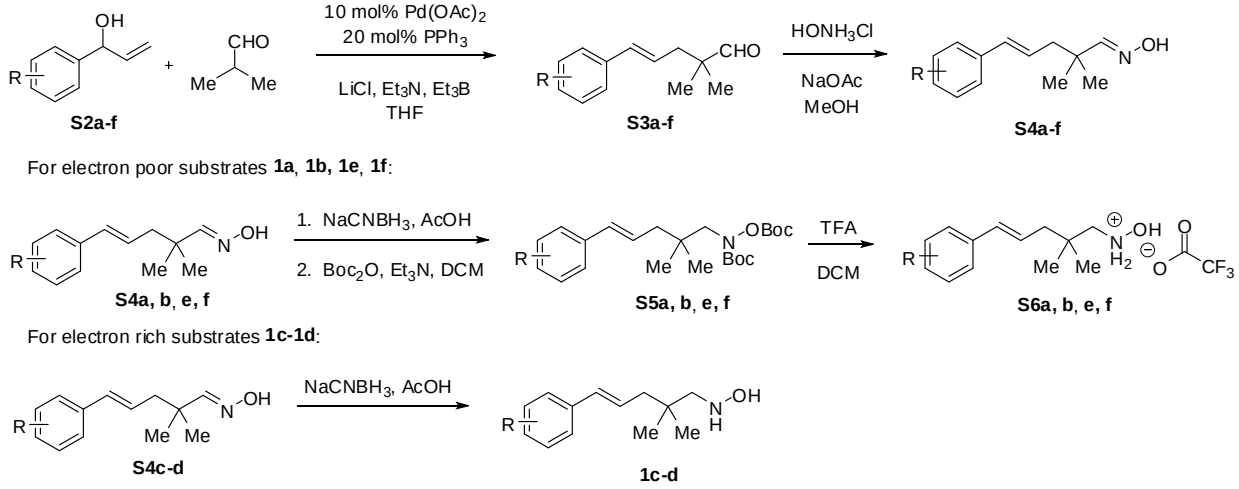
**4e**

**1-((*S*)-3,3-dimethyl-1-oxo-1-((*R*)-2-(pyren-4-yl)pyrrolidin-1-yl)butan-2-yl)-3-((1*R*,2*R*)-2-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)thiourea (4e):** $[\alpha]_D^{25} = 90.0^o$ (c=0.30, $CHCl_3$); The compound exists as a 1.4:1 mixture of amide rotamers in $CDCl_3$. $^1H$ NMR (500MHz ,$CDCl_3$) major rotamer resonances δ = 8.31 (d, *J* = 7.8 Hz, 1 H), 8.25 - 7.97 (m, 5 H), 7.95 - 7.86 (m, 2 H), 7.84 (s, 1 H), 7.66 - 7.34 (m, 5 H), 6.14 (d, *J* = 8.2 Hz, 1 H), 6.01 (d, *J* = 3.2 Hz, 1 H), 5.94 (d, *J*

= 2.7 Hz, 1 H), 5.55 (d, *J* = 9.2 Hz, 2 H), 4.82 (t, *J* = 8.5 Hz, 1 H), 4.06 - 3.81 (m, 3 H), 2.39 (s, 3 H), 2.23 - 1.49 (m, 12 H), 1.16 - 1.10 (m, 9 H); $^{13}$C NMR (126MHz ,$CDCl_3$) major and minor resonances δ = 182.1, 182.0, 172.1, 170.2, 137.2, 136.2, 135.3, 134.4, 131.6, 131.4, 130.9, 130.4, 129.9, 129.8, 129.0, 128.9, 128.6, 128.4, 127.6, 127.4, 127.2, 127.0, 126.0, 125.8, 125.8, 125.7, 125.5, 125.3, 125.3, 125.2, 124.9, 124.8, 124.6, 124.1, 123.9, 123.0, 122.3, 120.8, 110.6, 109.9, 108.8, 63.2, 61.5, 60.1, 59.7, 59.4, 58.5, 56.2, 55.8, 48.5, 47.0, 36.0, 35.7, 35.3, 34.6, 34.5, 33.7, 33.5, 32.3, 29.7, 29.0, 26.9, 26.6, 26.2, 25.7, 25.4, 25.2, 24.7, 24.3, 23.5, 21.8, 20.7, 18.7, 15.5; FTIR: 3396 (m), 3280 (w), 3054 (m), 2962 (m), 2870 (w), 1638 (s), 1610 (s), 1520 (s), 1445 (s), 1311 (m); LRMS $[M+Na]^+$ calculated for $C_{44}H_{48}N_4NaOS$: 703.34, found: 703.2

## 3. Substrate Preparation and Characterization Data

**General synthetic route for the preparation of substrates 1a-1f.**




## General Procedure:

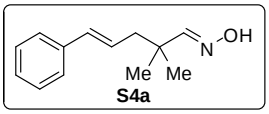
Branched allylic alcohols **S2a-f** were synthesized via previously reported methods. The spectral data matched those reported in the literature.[3]

**Tsuji-Trost Allylation:**[4] To a solution of palladium acetate (112 mg, 0.5 mmol), triphenylphosphine (262 mg, 1.0 mmol) and lithium chloride (211 mg, 5.0 mmol) in dry tetrahydrofuran (5 mL) were successively added isobutyraldehyde (500 μL, 5.5 mmol), branched allylic alcohol **S2a-f** (5.0 mmol), triethylamine (836 μL, 6.0 mmol), and triethylborane (12 mmol, 1.0 M solution in hexanes) via syringe at ambient temperatures under nitrogen. The mixture was stirred at ambient temperature for 48 h. The mixture was filtered through a Celite pad and washed with ethyl acetate. The filtrate was washed with saturated aqueous sodium bicarbonate, and the organic phase was dried over magnesium sulfate, concentrated in vacuo and carried forward to the following reaction without further purification.

[3] (a) Bouziane, A.; Helou, M.; Carboni, B.; Carreaux, F.; Demerseman, B.; Bruneau, C.; Renaud, J. *Chem. Eur. J.* **2008**, *14*, 5630-5637. (b) Logan, A. W. J.; Parker, J. S.; Hallside, M. S.; Burton, J. W. *Org. Lett.* **2012**, *14*, 2940. (c) Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3470.

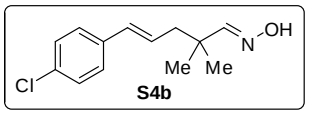
[4] Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401.

**Oxime formation:** To aldehyde **S3a-f** (5.0 mmol) in a solution of methanol (50 mL) was added hydroxylamine hydrochloride (870 mg, 12.5 mmol) and sodium acetate (1.025 g, 12.5 mmol). A reflux condenser was fitted to the flask, and the mixture heated at reflux for 14 h. Upon cooling to ambient temperature, water (~50 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3 x 25 mL). The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired oxime **S4a-f**.



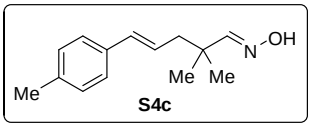
**S4a**

**(1*E*,4*E*)-2,2-dimethyl-5-phenylpent-4-enal oxime (S4a).** Following the general procedure (850 mg, 84% yield over 2 steps) of the desired product was isolated as a clear oil. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 8.12 (s, 1 H), 7.43 (s, 1 H), 7.37 (d, *J* = 7.8 Hz, 2 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 6.44 (d, *J* = 15.6 Hz, 1 H), 6.20 (td, *J* = 7.3, 15.6 Hz, 1 H), 2.34 (d, *J* = 7.3 Hz, 2 H), 1.17 (s, 6 H); $^{13}$C NMR (126MHz , $CDCl_3$) δ = 158.6, 137.4, 133.2, 128.5, 127.1, 126.1, 125.6, 44.4, 37.2, 25.2; FTIR: 3319 (br), 3027 (w), 2965 (m), 2925 (w), 1598 (w), 1496 (m), 1449 (s), 967 (s), 942 (s); LRMS $[M+H]^+$ calculated for $C_{13}H_{18}NO$: 238.09, found: 238.1



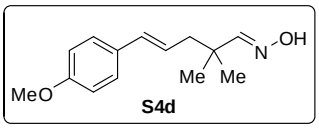
**S4b**

**(1*E*,4*E*)-5-(4-chlorophenyl)-2,2-dimethylpent-4-enal oxime (S4b).** Following the general procedure (1.01 g, 85% yield over 2 steps) of the desired product was isolated as a white solid. $^{1}$H NMR (500MHz , $CDCl_3$) δ = 8.03 (s, 1 H), 7.40 (s, 1 H), 7.28 (s, 4 H), 6.37 (d, *J* = 16.0 Hz, 1 H), 6.16 (td, *J* = 7.3, 16.0 Hz, 3 H), 2.33 (dd, *J* = 1.4, 7.3 Hz, 2 H), 1.15 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 158.4, 135.8, 132.7, 132.0, 128.6, 127.3, 126.5, 44.3, 37.2, 25.2; FTIR: 3325 (br), 3028 (w), 2967 (s), 2926 (m), 1652 (w), 1594 (w), 1491 (s), 1095 (s); LRMS $[M+H]^+$ calculated for $C_{13}H_{17}ClNO$: 204.13, found: 204.1



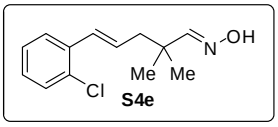
**S4c**

**(1*E*,4*E*)-2,2-dimethyl-5-p-tolylpent-4-enal oxime (S4c).** Following the general procedure (870 mg, 80% yield over 2 steps) of the desired product was isolated as a white solid. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 8.60 - 7.97 (br. s, 1 H), 7.42 (s, 1 H), 7.27 (d, *J* = 7.8 Hz, 2 H), 7.13 (d, *J* = 8.3 Hz, 2 H), 6.40 (d, *J* = 15.6 Hz, 1 H), 6.15 (td, *J* = 7.6, 15.5 Hz, 1 H), 2.35 (s, 3 H), 2.33 (dd, *J* = 1.2, 7.6 Hz, 2 H), 1.16 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 158.6, 136.9, 134.6, 133.0, 129.2, 126.0, 124.5, 44.4, 37.2, 25.1, 21.1; FTIR: 3284 (m), 2966 (s), 2923 (m), 2869 (m), 1510 (m), 1453 (m), 1427 (m), 1309 (m); LRMS $[M+H]^+$ calculated for $C_{14}H_{20}NO$: 218.15, found: 218.1



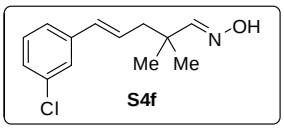
**S4d**

**(1*E*,4*E*)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-enal oxime (S4d).** Following the general procedure (865 mg, 74% yield over 2 steps) of the desired product was isolated as a white solid. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 8.19 (s, 1 H), 7.42 (s, 1 H), 7.30 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.37 (d, *J* = 15.6 Hz, 1 H), 6.05 (td, *J* = 7.3, 15.6 Hz, 1 H), 3.82 (s, 3 H), 2.31 (d, *J* = 7.8 Hz, 2 H), 1.15 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 158.9, 158.6, 132.5, 130.2, 127.2, 123.4, 113.9, 55.3, 44.4, 37.2, 25.1; FTIR: 3318 (br), 2964 (m), 2836 (w), 1607 (m), 1510 (s), 1463 (m), 1299 (m), 1246 (s); LRMS $[M+H]^+$ calculated for $C_{14}H_{20}NO_2$: 234.14, found: 234.1



S4e

**(1*E*,4*E*)-5-(2-chlorophenyl)-2,2-dimethylpent-4-enal oxime (S4e).** Following the general procedure (825 mg, 69% yield over 2 steps) of the desired product was isolated as a white solid. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 7.98 (s, 1 H), 7.50 (dd, *J* = 1.8, 7.8 Hz, 1 H), 7.43 (s, 1 H), 7.35 (dd, *J* = 1.4, 7.8 Hz, 1 H), 7.19 (dtd, *J* = 1.4, 7.3, 23.8 Hz, 2 H), 6.80 (d, *J* = 16.0 Hz, 1 H), 6.17 (td, *J* = 7.3, 15.1 Hz, 1 H), 2.39 (dd, *J* = 0.9, 7.8 Hz, 2 H), 1.17 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 158.5, 135.6, 132.6, 129.6, 129.5, 128.8, 128.2, 126.9, 126.7, 44.4, 37.1, 25.2; FTIR: 3314 (br), 2966 (m), 2927 (w), 1649 (w), 1470 (s), 1440 (s), 1384 (m); LRMS $[M+H]^+$ calculated for $C_{13}H_{18}NO$: 238.09, found: 238.1



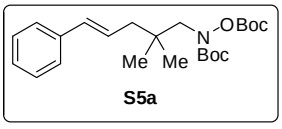
S4f

**(1*E*,4*E*)-5-(3-chlorophenyl)-2,2-dimethylpent-4-enal oxime (S4f).** Following the general procedure (980 mg, 82% yield over 2 steps) of the desired product was isolated as a white solid. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 7.76 (s, 1 H), 7.41 (s, 1 H), 7.35 (s, 1 H), 7.26 - 7.17 (m, 3 H), 6.36 (d, *J* = 15.6 Hz, 1 H), 6.21 (td, *J* = 7.8, 15.6 Hz, 1 H), 2.34 (d, *J* = 7.8 Hz, 2 H), 1.16 (s, 6 H); $^{13}$C NMR (126MHz , $CDCl_3$) δ = 158.5, 139.2, 134.4, 131.9, 129.7, 127.5, 127.1, 126.0, 124.4, 44.2, 37.1, 25.3; FTIR: 3319 (br), 2966 (s), 2927 (m), 1651 (w), 1594 (s), 1568 (s), 1474 (s), 1426 (s); LRMS $[M+H]^+$ calculated for $C_{13}H_{18}NO$: 238.09, found: 238.1

**Oxime reduction:** A solution of oxime **S4a**, **b**, **e**, or **f** (1.5 mmol) in acetic acid (2.5 mL) was cooled to 15 ºC, and sodium cyanoborohydride (188 mg, 3.0 mmol) was added in one portion. After stirring at 15 ºC for 5 mins, the mixture was warmed to 23 ºC and stirred for 1 h. The reaction was quenched by the addition of 20% aq. potassium carbonate (20 mL) and extracted with diethyl ether. The organics were washed with 20% aq. potassium carbonate (20 mL) dried over magnesium sulfate, concentrated *in vacuo* and carried forward to the following reaction without further purification.

***To prevent excessive thermal cyclization, the hydroxylamine must be subjected to the Boc protection conditions immediately following workup.***

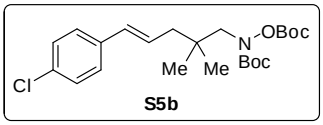
**Boc protection:** To crude hydroxylamine **1a**, **b**, **e**, or **f** (1.5 mmol) in a solution of dichloromethane (10 mL) was added di-*tert*-butyl dicarbonate (1.3 g, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol). The mixture was stirred at 23 ºC for 14 h. Water (20 mL) was added, and the organics were extracted with dichloromethane (2 x 25 mL), washed with 1M HCl (25 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel to give the desired Boc-protected hydroxylamine **S5a**, **b**, **e**, or **f**.



S5a

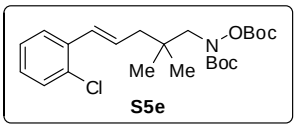
**(*E*)-*tert*-butyl (*tert*-butoxycarbonyl)oxy(2,2-dimethyl-5-phenylpent-4-en-1-yl)carbamate (S5a).** Following the general procedure on a 3.5 mmol scale (1.18 g, 83% yield over 2 steps) of the desired product was isolated as a clear oil. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 7.36 (d, *J* = 7.3 Hz, 2 H), 7.30 (t, *J* = 7.6 Hz, 2 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 6.41 (d, *J* = 16.0 Hz, 1 H), 6.25 (td, *J* = 7.3, 16.0 Hz, 1 H), 3.69 (br. s, 1 H), 3.30 (br. s, 1 H), 2.21 (d, *J* = 7.3 Hz, 2 H), 1.53 (s, 9 H), 1.48 (s, 9 H), 0.99 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 155.3, 152.2, 137.7, 132.7, 128.4, 126.9, 126.7, 126.0, 84.8, 82.1, 60.3, 43.5, 35.8, 28.1, 27.6, 25.3; FTIR: 2979 (m), 2933 (w),

1781 (s), 1719 (s), 1369 (s), 1249 (s); LRMS $[M+Na]^+$ calculated for $C_{23}H_{35}NNaO_5$: 428.24, found: 428.1



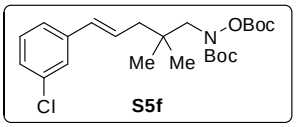
**S5b**

**(*E*)-*tert*-butyl (*tert*-butoxycarbonyl)oxy(5-(4-chlorophenyl)-2,2-dimethylpent-4-en-1-yl)carbamate (S5b).** Following the general procedure on a 1.0 mmol scale (220 mg, 50% yield over 2 steps) of the desired product was isolated as a clear oil. $^1$H NMR (500MHz ,$CDCl_3$) δ = 7.29 - 7.22 (m, 4 H), 6.35 (d, *J* = 15.6 Hz, 1 H), 6.22 (td, *J* = 7.6, 15.5 Hz, 1 H), 3.65 (br. s, 1 H), 3.25 (br. s, 1 H), 2.19 (d, *J* = 7.3 Hz, 2 H), 1.51 (s, 9 H), 1.47 (s, 9 H), 0.97 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 155.3, 152.2, 136.2, 132.4, 131.5, 128.6, 127.6, 127.2, 84.8, 82.2, 60.3, 43.5, 35.8, 28.1, 27.6, 25.3; FTIR: 2978 (m), 2932 (w), 1782 (s), 1718 (s), 1491 (w), 1370 (s), 1248 (s); LRMS $[M+Na]^+$ calculated for $C_{23}H_{35}ClNNaO_5$: 462.20, found: 462.1



**S5e**

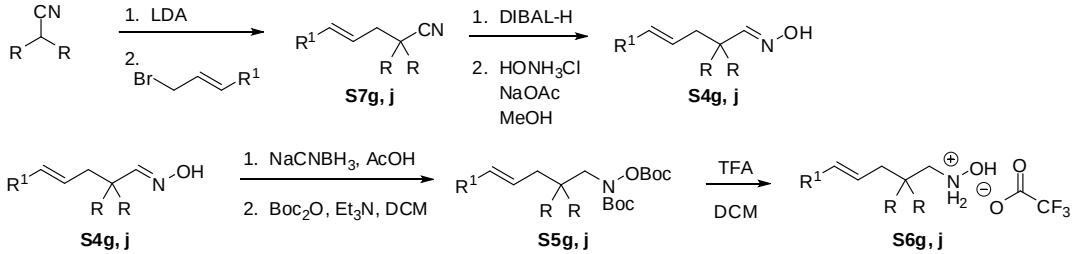
**(*E*)-*tert*-butyl (*tert*-butoxycarbonyl)oxy(5-(2-chlorophenyl)-2,2-dimethylpent-4-en-1-yl)carbamate (S5e).** Following the general procedure on a 1.0 mmol scale (257 mg, 58% yield over 2 steps) of the desired product was isolated as a clear oil. $^1$H NMR (500MHz ,$CDCl_3$) δ = 7.51 (d, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.20 (t, *J* = 6.8 Hz, 1 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 6.77 (d, *J* = 15.6 Hz, 1 H), 6.23 (td, *J* = 7.6, 15.5 Hz, 1 H), 3.67 (br. s, 1 H), 3.27 (br. s, 1 H), 2.25 (d, *J* = 7.8 Hz, 2 H), 1.52 (s, 9 H), 1.49 (s, 9 H), 1.00 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 155.3, 152.2, 135.9, 132.5, 129.9, 129.5, 129.0, 127.9, 126.8, 126.7, 84.8, 82.2, 60.4, 43.6, 35.8, 28.1, 27.6, 25.3; FTIR: 2980 (m), 2932 (m), 1782 (s), 1719 (s), 1471 (m), 1370 (s), 1254 (s); LRMS $[M+Na]^+$ calculated for $C_{23}H_{35}ClNNaO_5$: 462.20, found: 462.1



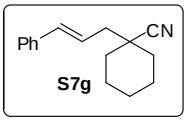
**S5f**

**(*E*)-*tert*-butyl (*tert*-butoxycarbonyl)oxy(5-(3-chlorophenyl)-2,2-dimethylpent-4-en-1-yl)carbamate (S5f).** Following the general procedure (361 mg, 55% yield over 2 steps) of the desired product was isolated as a clear oil. $^1$H NMR (500MHz ,$CDCl_3$) δ = 7.34 (s, 1 H), 7.25 - 7.19 (m, 2 H), 7.19 - 7.14 (m, 1 H), 6.35 (d, *J* = 15.6 Hz, 1 H), 6.26 (td, *J* = 7.3, 15.6 Hz, 1 H), 3.65 (br. s, 1 H), 3.26 (br. s, 1 H), 2.21 (d, *J* = 6.4 Hz, 2 H), 1.52 (s, 9 H), 1.49 (s, 9 H), 0.98 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 155.3, 152.2, 139.6, 134.4, 131.4, 129.6, 128.5, 126.8, 125.9, 124.3, 84.9, 82.2, 60.3, 43.4, 35.8, 28.1, 27.6, 25.3; FTIR: 2979 (m), 2933 (w), 1780 (s), 1717 (s), 1594 (m), 1568 (w), 1475 (m), 1426 (m), 1369 (s); LRMS $[M+Na]^+$ calculated for $C_{23}H_{35}ClNNaO_5$: 462.20, found: 462.1

**General synthetic route for the preparation of substrates 1g and 1j.**



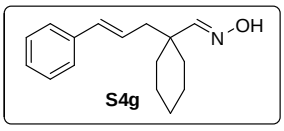
**Nitrile alkylation:** To a flame-dried 100 mL round-bottom flask was added diisopropyl amine (1.4 mL, 10 mmol) and tetrahydrofuran (20 mL) under nitrogen. The mixture was cooled to -78 ºC, and *n*BuLi (4.2 mL of a 2.5 M solution in hexanes, 10.5 mmol) was added dropwise. The mixture was warmed to 0 ºC and stirred for 10 minutes, then cooled to -78 ºC. The nitrile (10 mmol) was then added dropwise as a solution in tetrahydrofuran (5 mL), and the mixture was warmed to 0 ºC and stirred for 5 minutes. The bromide (12 mmol) was then added as a solution in tetrahydrofuran (5 mL), and the mixture was warmed to 23 ºC and stirred for 14 h. The reaction was quenched by the addition of water (25 mL) and extracted with diethyl ether (3 x 25 mL). The organics were washed with water (25 mL) and brine (25 mL), dried over magnesium sulfate, and concentrated *in vacuo*. **S7g** was purified by flash chromatography on silica gel. **S7j** (2,2-dimethylpent-4-enenitrile) was carried on to the following reaction without further purification.




**1-cinnamylcyclohexanecarbonitrile (S7g):** Following the general procedure, the alkylation was performed on a 10 mmol scale, and the desired product was isolated as a clear oil (1.82 g, 81% yield). The spectral data matched those reported in the literature.[5]

**Nitrile reduction:** In a flame-dried 100 mL round-bottom flask a solution of nitrile (8.1 mmol) in tetrahydrofuran (20 mL) was cooled to -78 ºC. A solution of diisobutylaluminum hydride (12.2 mL of a 1.0 M solution in hexanes, 12.2 mmol) was added dropwise. The mixture was stirred at -78 ºC for 15 minutes, and warmed to 23 ºC and stirred for 2 h. The mixture was cooled to 0 ºC and 1 M aq. HCl was added (20 mL). Diethyl ether was added, and the mixture was stirred for 1 h at 23 ºC. The phases were separated, and the aqueous phase was extracted with diethyl ether (2 x 25). The combined organics were dried over magnesium sulfate, and concentrated *in vacuo* to yield the aldehyde product, which was carried on to the following reaction without further purification.

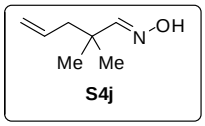
**Oxime formation:** To the crude aldehyde (8.1 mmol) in a solution of methanol (65 mL) was added hydroxylamine hydrochloride (1.4 g, 20.25 mmol) and sodium acetate (1.7 g, 20.25 mmol). A reflux condenser was fitted to the flask, and the mixture heated at reflux for 14 h. Upon cooling to ambient temperature, water (~80 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3 x 35 mL). The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired oxime.




**(*E*)-1-cinnamylcyclohexanecarbaldehyde oxime (S4g):** Following the general procedure (1.81 g, 92% over 2 steps) of the desired product was isolated as a clear oil. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 7.97 (s, 1 H), 7.37 - 7.34 (m, 2 H), 7.33 (s, 1 H), 7.32 - 7.28 (m, 2 H), 7.24 - 7.19 (m, 1 H), 6.41 (d, *J* = 15.6 Hz, 1 H), 6.18 (td, *J* = 7.3, 15.1 Hz, 1 H), 2.35 (d, *J* = 7.3 Hz, 2 H), 1.83 - 1.69 (m, 2 H), 1.62 - 1.25 (m, 8 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 157.8, 137.5, 132.9, 128.4, 127.1, 126.1, 125.5, 43.5, 40.6, 34.2, 26.0, 22.1; FTIR: 3320 (m), 3026 (m), 2926 (s), 2852 (m),

[5] Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200.

1649 (w), 1598 (w), 1495 (m), 1448 (s), 1305 (m); LRMS $[M+H]^+$ calculated for $C_{16}H_{22}NO$: 244.16, found 244.2



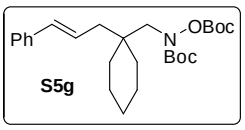
**S4j**

**(*E*)-2,2-dimethylpent-4-enal oxime (S4j):** Following the general procedure the desired product was isolated as a clear oil. $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.77 (br. s, 1 H), 7.35 (s, 1 H), 5.76 (m, 1H), 5.14 - 4.97 (m, 2 H), 2.16 (d, *J* = 7.3 Hz, 2 H), 1.09 (s, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 158.4, 133.8, 118.1, 45.2, 36.6, 25.0; FTIR: 3327 (br), 3078 (m), 2968 (s), 2910 (m), 1641 (m), 1462 (m), 1436 (m), 1384 (m), 1366 (m); LRMS $[M+H]^+$ calculated for $C_7H_{14}NO$: 128.10, found 128.1

**Oxime reduction:** A solution of oxime **S4g**, or **j** (1.5 mmol) in acetic acid (2.5 mL) was cooled to 15 ºC, and sodium cyanoborohydride (188 mg, 3.0 mmol) was added in one portion. After stirring at 15 ºC for 5 mins, the mixture was warmed to 23 ºC and stirred for 1 h. The reaction was quenched by the addition of 20% aq. potassium carbonate (20 mL) and extracted with diethyl ether. The organics were washed 20% aq. potassium carbonate (20 mL), dried over magnesium sulfate, concentrated *in vacuo* and carried forward to the following reaction without further purification.

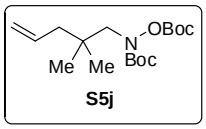
***To prevent excessive thermal cyclization, the hydroxylamine must be subjected to the Boc protection conditions immediately following workup.***

**Boc protection:** To crude hydroxylamine **1g** or **j** (1.5 mmol) in a solution of dichloromethane (10 mL) was added di-*tert*-butyl dicarbonate (1.3 g, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol). The mixture was stirred at 23 ºC for 14 h. Water (20 mL) was added, and the organics were extracted with dichloromethane (2 x 25 mL), washed with 1M HCl (25 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel to give the desired Boc-protected hydroxylamine **S5g** or **j**.



**S5g**

**(*E*)-*tert*-butyl (*tert*-butoxycarbonyl)oxy((1-cinnamylcyclohexyl)methyl)carbamate (S5g):** Following the general procedure (417 mg, 62% yield over 2 steps) of the desired product was isolated as a clear oil. $^1$H NMR (500MHz ,$CDCl_3$) δ = 7.35 (d, *J* = 7.3 Hz, 2 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.19 (t, *J* = 6.8 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 6.26 (td, *J* = 7.6, 15.5 Hz, 1 H), 3.84 - 3.70 (m, 1 H), 3.38 - 3.25 (m, 1 H), 2.30 (d, *J* = 7.3 Hz, 2 H), 1.50 (s, 9 H), 1.48 (s, 9 H), 1.47 - 1.32 (m, 10 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 155.5, 152.3, 137.9, 132.6, 128.4, 126.8, 126.6, 126.0, 84.8, 82.2, 57.3, 39.3, 37.9, 34.1, 33.6, 33.3, 28.1, 27.6, 26.1, 21.5; FTIR: 2980 (m), 2928 (m), 2855 (w), 1778 (s), 1715 (s), 1599 (w), 1455 (m), 1392 (m), 1369 (s), 1236 (s); LRMS $[M+Na]^+$ calculated for $C_{26}H_{39}NNaO_5$: 468.27, found 468.2

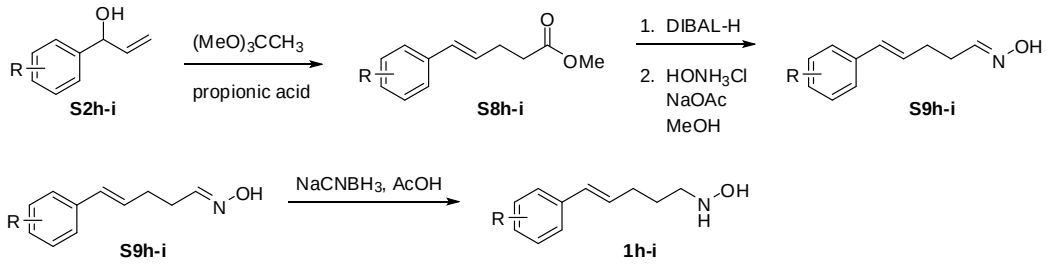


**S5j**

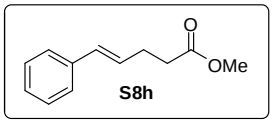
***tert*-butyl (*tert*-butoxycarbonyl)oxy(2,2-dimethylpent-4-en-1-yl)carbamate (S5j):** Following the general procedure on a 4.7 mmol scale (562 mg, 36% yield over 2 steps) of the desired product was isolated as a clear oil. $^1$H NMR (500MHz, $CDCl_3$) δ = 5.81 (s, 1 H), 5.09 - 4.95 (m, 2 H), 3.60 (br. s, 1 H), 3.22 (br. s, 1 H), 1.54 (s, 9 H), 1.47 (s, 9 H), 0.93 - 0.90 (m, 6 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 155.2, 152.2, 134.8, 117.4, 84.7, 82.1, 60.2, 44.5, 35.0, 28.1, 27.6, 25.1; FTIR: 3078 (m), 2982

(m), 1781 (s), 1715 (s), 1370 (s), 1248 (s); LRMS $[M+Na]^+$ calculated for $C_{17}H_{31}NNaO_5$: 352.21, found 352.1

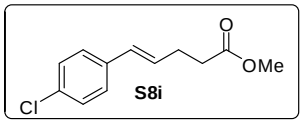
**General synthetic route for the preparation of substrates 1h-1i.**




Branched allylic alcohols **S2h-i** were synthesized via previously reported methods. The spectral data matched those reported in the literature.[3]




**(*E*)-methyl 5-phenylpent-4-enoate (S8h):** Prepared by previously reported methods. The spectral data matched those reported in the literature.[6]



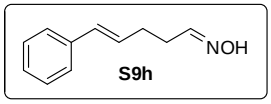

**(*E*)-methyl 5-(4-chlorophenyl)pent-4-enoate (S8i):** To 1-(4-chlorophenyl)prop-2-en-1-ol (169 mg, 1.0 mmol) in a microwave vial was added trimethyl orthoacetate (0.673 mL, 5.0 mmol) and propionic acid (2 drops, catalytic). The vial was sealed, and heated at 140 ºC for 14 h. The mixture was cooled, and purified by flash chromatography on silica gel to give the desired ester product (128 mg, 57% yield) as a white solid. $^1$H NMR (500MHz ,$CDCl_3$) $\delta$ = 7.26 (s, 4 H), 6.39 (d, *J* = 15.6 Hz, 1 H), 6.19 (td, *J* = 6.7, 15.9 Hz, 1 H), 3.70 (s, 3 H), 2.58 - 2.46 (m, 4 H); $^{13}$C NMR (126MHz ,$CDCl_3$) $\delta$ = 173.3, 135.8, 132.7, 129.8, 129.1, 128.6, 127.3, 51.6, 33.7, 28.2; FTIR: 3031 (w), 2951 (m), 1739 (s), 1492 (s), 1437 (m), 1169 (m)

**Ester reduction:** To a solution of ester (2.5 mmol) in dichloromethane (10 mL) at -78 ºC was added diisobutylaluminum hydride (2.75 mL of a 1.0 M solution in hexanes, 2.75 mmol) dropwise. The mixture was stirred for 1 h at -78 ºC. A saturated solution of Rochelle's salt (15 mL) was added, and the mixture was warmed to 23 ºC and stirred until a separation of phases was observed. The organics were extracted with dichloromethane (2 x 25 mL), dried over sodium sulfate, concentrated *in vacuo* and carried forward to the following reaction without further purification.

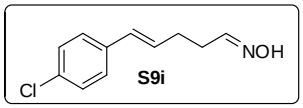
**Oxime formation:** To the crude aldehyde (2.5 mmol) in a solution of methanol (20 mL) was added hydroxylamine hydrochloride (434 mg, 6.25 mmol) and sodium acetate (513 mg, 6.25 mmol). A reflux condenser was fitted to the flask, and the mixture heated at reflux for 14 h. Upon cooling to ambient temperature, water (~30 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3 x 15 mL). The organic phase was dried over

[6] Blunt, A. J.; Bailey, C. D.; Cons, B. D.; Edwards, S. J.; Elsworth, J. D.; Pheko, T.; Willis, C. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 3901.

sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired oxime.

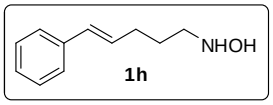



**(4*E*)-5-phenylpent-4-enal oxime (S9h):** Following the general procedure on a 2.9 mmol scale, the desired product (400 mg, 79% yield over two steps) was isolated as a white solid as a 3.5:1 mixture of oxime isomers. The following NMR data is for the major isomer. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 8.75 (br. s., 1 H), 7.39 - 7.34 (m, 2 H), 7.33 - 7.29 (m, 2 H), 7.25 - 7.19 (m, 1 H), 6.80 (t, *J* = 5.3 Hz, 1 H), 6.46 (d, *J* = 16.0 Hz, 1 H), 6.22 (td, *J* = 6.7, 15.9 Hz, 1 H), 2.59 (dt, *J* = 5.5, 7.3 Hz, 2 H), 2.48 - 2.37 (m, 2 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 151.8, 137.3, 130.9, 128.7, 128.5, 127.1, 126.0, 29.3, 24.5; FTIR: 3189 (s), 3083 (s), 3027 (s), 2869 (s), 1666 (m), 1596 (w), 1577 (w), 1490 (s), 1320 (m), 1233 (m); LRMS $[M+H]^+$ calculated for $C_{11}H_{14}NO$: 176.10, found 176.2

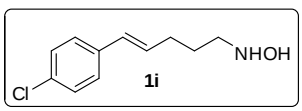



**(4*E*)-5-(4-chlorophenyl)pent-4-enal oxime (S9i):** Following the general procedure on a 4.9 mmol scale, the desired product (800 mg, 78% yield over two steps) was isolated as a white solid. $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 7.94 - 7.76 (m, 1 H), 7.31 - 7.23 (m, 4 H), 6.79 (t, *J* = 5.5 Hz, 1 H), 6.42 (d, *J* = 15.6 Hz, 1 H), 6.20 (td, *J* = 6.8, 15.7 Hz, 1 H), 2.59 (dt, *J* = 5.5, 7.3 Hz, 2 H), 2.44 (q, *J* = 7.3 Hz, 2 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 152.1, 136.1, 133.0, 130.0, 129.7, 128.9, 127.5, 29.5, 24.6; FTIR: 3188 (m), 3087 (m), 3037 (m), 2874 (m), 1896 (w), 1723 (m), 1666 (m), 1594 (m), 1490 (s), 1445 (m), 1406 (m), 1352 (m); LRMS $[M+H]^+$ calculated for $C_{11}H_{13}ClNO$: 210.06, found 210.1

**Oxime reduction:** A solution of oxime **S9h**, or **i** (1.5 mmol) in acetic acid (2.5 mL) was cooled to 15 ºC, and sodium cyanoborohydride (188 mg, 3.0 mmol) was added in one portion. After stirring at 15 ºC for 5 mins, the mixture was warmed to 23 ºC and stirred for 1 h. The reaction was quenched by the addition of 20% aq. potassium carbonate (20 mL) and extracted with diethyl ether. The organics were washed with 20% aq. potassium carbonate (20 mL) dried over magnesium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired hydroxylamine product.




**(*E*)-N-(5-phenylpent-4-en-1-yl)hydroxylamine (1h):** Following the general procedure on a 2.3 mmol scale, the desired product was isolated as a white solid (195 mg, 48% yield). $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 7.37 - 7.33 (m, 2 H), 7.33 - 7.28 (m, 2 H), 7.23 - 7.19 (m, 1 H), 6.42 (d, *J* = 15.6 Hz, 1 H), 6.22 (td, *J* = 7.1, 15.6 Hz, 1 H), 3.01 (t, *J* = 7.1 Hz, 2 H), 2.29 (q, *J* = 6.9 Hz, 2 H), 1.76 (quin, *J* = 7.3 Hz, 2 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 137.6, 130.4, 129.9, 128.5, 126.9, 125.9, 53.3, 30.5, 26.6; FTIR: 3265 (m), 3246 (m), 3122 (m), 3024 (m), 2944 (m), 2836 (m), 1513 (w), 1492 (m), 1451 (s), 1436 (m), 1374 (m), 1146 (m); LRMS $[M+H]^+$ calculated for $C_{11}H_{16}NO$: 178.12, found 178.2

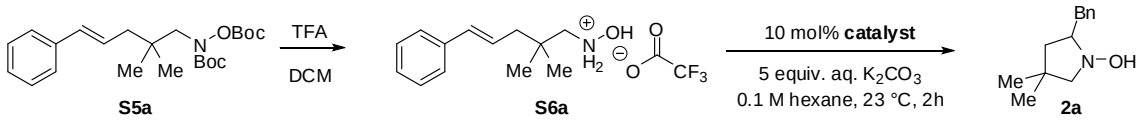



**(*E*)-N-(5-(4-chlorophenyl)pent-4-en-1-yl)hydroxylamine (1i):** Following the general procedure on a 3.8 mmol scale, the desired product was isolated as a white solid (270 mg, 34% yield). $^{1}$H NMR (500MHz ,$CDCl_3$) δ = 7.26 (s, 4 H), 6.36 (d, *J* = 16.0 Hz, 1 H), 6.19 (td, *J* = 6.9, 16.0 Hz, 1 H), 3.00 (t, *J* = 7.1 Hz, 2 H), 2.28 (q, *J* = 7.3 Hz, 2 H), 1.74 (quin, *J* = 7.3 Hz, 2 H); $^{13}$C NMR

(126MHz ,$CDCl_3$) δ = 136.1, 132.5, 130.7, 129.2, 128.6, 127.1, 53.3, 30.5, 26.6; FTIR: 3278 (m), 3149 (m), 2929 (s), 2828 (s), 1592 (w), 1544 (m), 1491 (s), 1432 (m), 1406 (m), 1371 (m); LRMS $[M+H]^+$ calculated for $C_{11}H_{15}ClNO$: 212.08, found 212.1

## 4. General Procedure for the Thiourea-Catalyzed Cope-Type Hydroamination

Due to rapid thermal cyclization of hydroxylamine substrates, in many cases the hydroxylamine starting materials were generated *in situ* from the corresponding trifluoroacetate salts by the addition of aqueous potassium carbonate. This was necessary for hydroxylamines **1a-b**, **1e-g** and **1j** (see methods A and B below).




**S5a** **S6a** **2a**

For hydroxylamines **1c-d**, it was not necessary to generate the hydroxylamine *in situ*, but they were not stable to purification by flash chromatography on silica gel. For these substrates, the hydroxylamine was generated from reduction of the parent oxime, and carried into the catalytic hydroamination without further purification (see method C below).

Hydroxylamines **1h-i** were stable to purification by flash chromatography. These substrates were generated from the reduction of the parent oxime, purified by flash chromatography on silica gel, and then subjected to the catalytic reaction conditions (see method D below).

**Method A (catalyst screening):**

**Deprotection:** To a solution of Boc-protected hydroxylamine **S5a** (101 mg, 0.25 mmol) in dichloromethane (2.4 mL) was added trifluoroacetic acid (0.6 mL). The mixture was stirred for 1 h at 23 ºC, then concentrated *in vacuo* to yield salt **S6a**. The salt was left under reduced pressure (~0.5 torr) for 1 h, and then dissolved in dichloromethane (2.25 mL). 0.5 mL of solution was added to each of four one-dram vials, and the contents of the vials were concentrated. To one vial, mesitylene was added as an internal standard, and the amount of salt in that vial was determined by $^1$H NMR (0.046-0.049 mmol), which provided the yield for the deprotection (85-90%) and the amount of salt in the remaining three vials for the catalyst screening reactions.

**Hydroamination:** To a one dram vial containing trifluoroacetate salt **S6a** (0.046 mmol) was added hexanes (0.46 mL) and catalyst (0.0046 mmol). 20% aq. potassium carbonate (0.153 mL, 0.23 mmol) was added, and the mixture was stirred ***vigorously*** for 2 h. The mixture was extracted with dichloromethane (3 x 3 mL). *p*-Nitrobenzoyl chloride (34 mg, 0.18 mmol) and triethylamine (0.05 mL, 0.36 mmol) were added to the combined organics, and the mixture was stirred for 2 h. 20% aq. potassium carbonate (5 mL) was added, and the organics were extracted with dichloromethane (3 x 5 mL), dried over sodium sulfate, and concentrated *in vacuo*. Mesitylene was added as an internal standard, and the yield was determined by $^1$H NMR. The

*O*-benzoylated product was purified by flash chromatography on silica gel and the enantiomeric excess was determined by HPLC analysis.

**Method B (synthetic scale for substrates 1a-b, 1e-g and 1j):**

**Deprotection:** To a solution of Boc-protected hydroxylamine **S5a** (0.3 mmol) in dichloromethane (2.4 mL) was added trifluoroacetic acid (0.6 mL). The mixture was stirred for 1 h at 23 ºC, then concentrated *in vacuo* to yield salt **S6a**. The salt was left under reduced pressure (~0.5 torr) for 1 h, and then dissolved in dichloromethane (1.25 mL). 0.1 mL of the solution was added to a one-dram vial, and 1.0 mL of the solution was added to a 10 mL round bottom flask. The contents of the vial and flask were concentrated. To the vial, mesitylene was added as an internal standard, and the amount of salt in that vial was determined by $^1$H NMR (0.025 mmol), which allowed for the determination of the amount of salt in the round bottom flask (0.25 mmol).

**Hydroamination:** To round bottom flask containing trifluoroacetate salt **S6a** (0.25 mmol) was added hexanes (2.5 mL) and catalyst **5** (16.7 mg, 0.025 mmol). The mixture was cooled to 0 ºC and 20% aq. potassium carbonate (0.864 mL, 1.25 mmol) was added. The mixture was stirred ***vigorously*** for 12 h at 3 ºC. The mixture was extracted with dichloromethane (3 x 10 mL). *p*-Nitrobenzoyl chloride (185 mg, 1.0 mmol) and triethylamine (0.279 mL, 2.0 mmol) were added to the combined organics, and the mixture was stirred for 2 h. 20% aq. potassium carbonate (10 mL) was added, and the organics were extracted with dichloromethane (3 x 10 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel.

**Method C (synthetic scale for substrates 1c-d):**

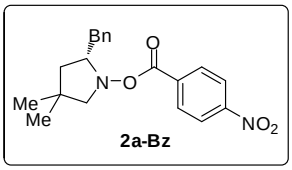
**Oxime reduction:** A solution of oxime **S4c** (0.6 mmol) in acetic acid (1.2 mL) was cooled to 15 ºC, and sodium cyanoborohydride (75 mg, 1.2 mmol) was added in one portion. After stirring at 15 ºC for 5 mins, the mixture was warmed to 23 ºC and stirred for 1 h. The reaction was quenched by the addition of ~10 mL aq. potassium carbonate (200 mg/mL) and extracted with diethyl ether. The organics were washed with ~10 mL aq. potassium carbonate (200 mg/mL) dried over magnesium sulfate and concentrated *in vacuo* to yield the desired hydroxylamine. The crude hydroxylamine was dissolved in diethyl ether (1.2 mL). 0.5 mL of solution was added to each of two 10 mL round bottom flasks, and the contents of the flasks were concentrated. Mesitylene was added to one of the flasks as an internal standard, and the amount of hydroxylamine (0.19 mmol) in that flask was determined by $^1$H NMR, which allowed for the determination of the amount of hydroxylamine (0.19 mmol) present in the other round bottom flask, which was ***immediately*** carried forward to the catalytic hydroamination.

**Hydroamination:** To round bottom flask dram vial containing hydroxylamine **1c** (0.19 mmol) was added hexanes (1.9 mL) and catalyst **5** (12.7 mg, 0.019 mmol). The mixture was stirred ***vigorously*** for 36 h at 3 ºC. To the mixture was added dichloromethane (10 mL), *p*-nitrobenzoyl chloride (141 mg, 0.76 mmol) and triethylamine (0.212 mL, 1.52 mmol), and the mixture was stirred for 2 h. 20% aq. potassium carbonate (10 mL) was added, and the organics were extracted with dichloromethane (3 x 10 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel.

**Method D (synthetic scale for substrates 1h-i):**

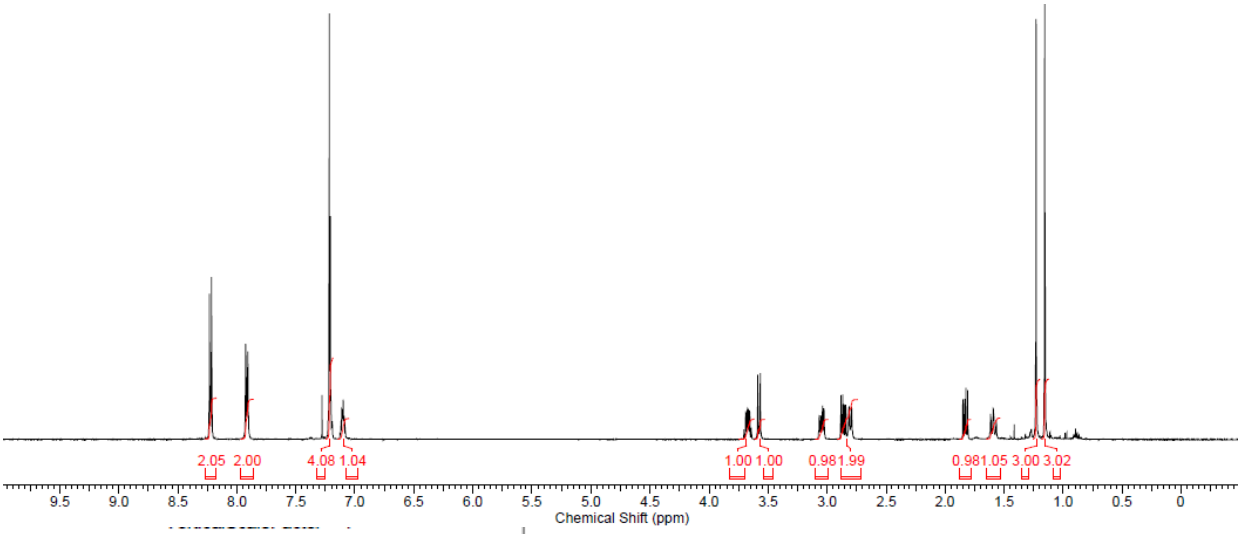
**Hydroamination:** To round bottom flask dram vial containing hydroxylamine **1h** (0.20 mmol) was added hexanes (2.0 mL) and catalyst **5** (13.4 mg, 0.02 mmol). The mixture was stirred ***vigorously*** for 36 h at 3 ºC. To the mixture was added dichloromethane (10 mL), *p*-nitrobenzoyl chloride (141 mg, 0.76 mmol) and triethylamine (0.212 mL, 1.52 mmol), and the mixture was stirred for 2 h. 20% aq. potassium carbonate (10 mL) was added, and the organics were extracted with dichloromethane (3 x 10 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel.

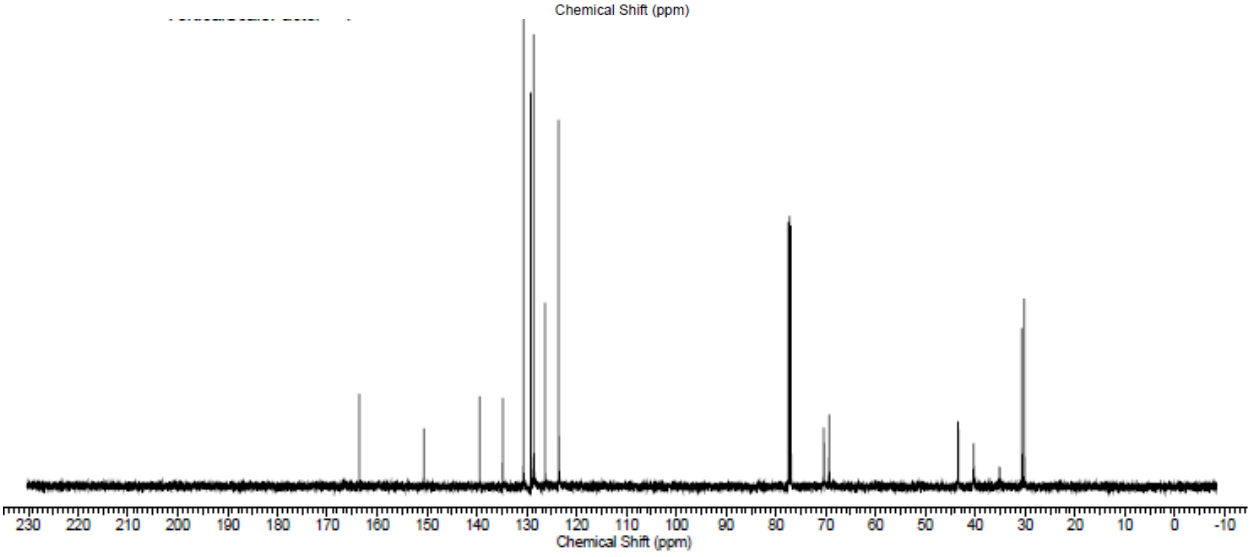
## 5. Characterization of Hydroamination Products



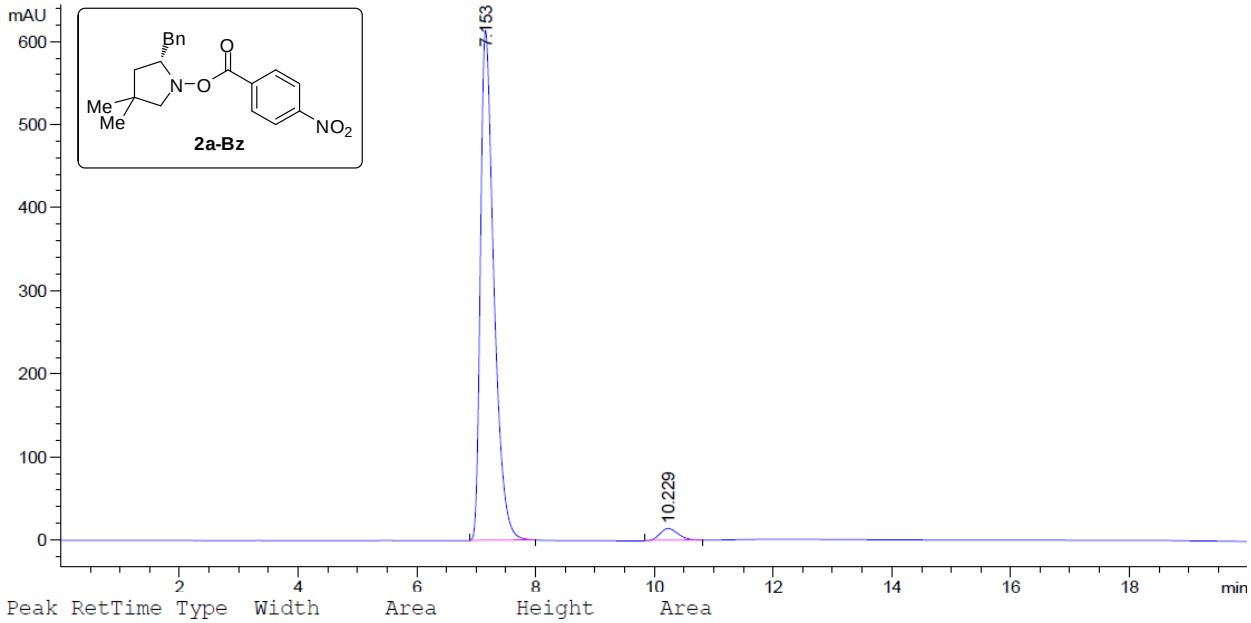
**2a-Bz**

**(*S*)-2-benzyl-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (2a-Bz):** According to the general procedure (method B), hydroxylamine **1a** (0.25 mmol) was reacted for 12 h to give the desired *O*-benzoylated hydroxylamine **2a-Bz** (74.0 mg, 83% yield) as a clear oil. $[\alpha]_D^{25}$=19.7 º (c=0.95, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.21 (d, *J* = 8.8 Hz, 2 H), 7.91 (d, *J* = 8.3 Hz, 2 H), 7.24 - 7.16 (m, 4 H), 7.14 - 7.03 (m, 1 H), 3.66 (qd, *J* = 6.9, 10.5 Hz, 1 H), 3.57 (d, *J* = 10.3 Hz, 1 H), 3.04 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.85 (dd, *J* = 7.1, 13.4 Hz, 1 H), 2.79 (d, *J* = 10.3 Hz, 1 H), 1.82 (dd, *J* = 7.3, 13.2 Hz, 1 H), 1.63 - 1.53 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.3, 150.3, 139.1, 134.6, 130.4, 129.0, 128.3, 126.1, 123.3, 70.1, 69.1, 43.2, 40.1, 34.9, 30.4, 29.9; FTIR (neat, $cm^{-1}$): 3110 (w), 3059 (w), 3028 (m), 2868 (m), 1742 (s), 1606 (m), 1526 (s), 1347 (s), 1259 (s); LRMS $[M+H]^+$ calculated for $C_{20}H_{22}N_2O_4$: 355.16, found: 355.2



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm), 94% ee

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|---|---|---|---|---|---|---|
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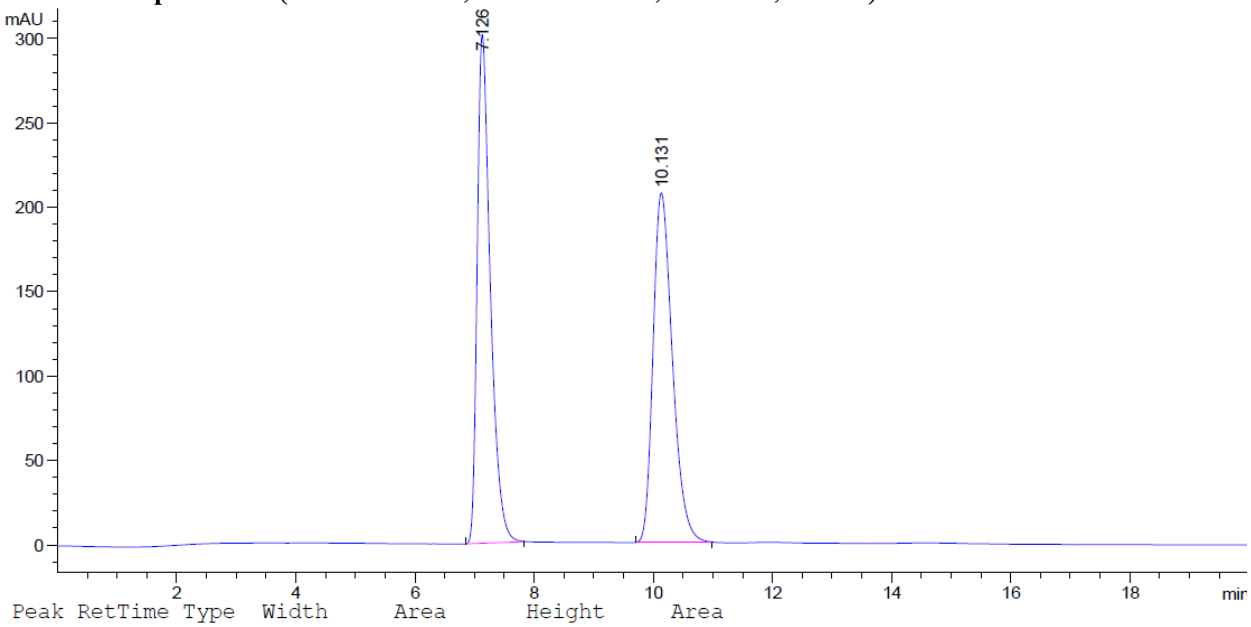
| 2 | 10.229 | BB | 0.3325 | 314.89047 | 14.55182 | 3.1536 |

**Racemic Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm)




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
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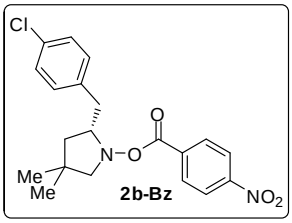
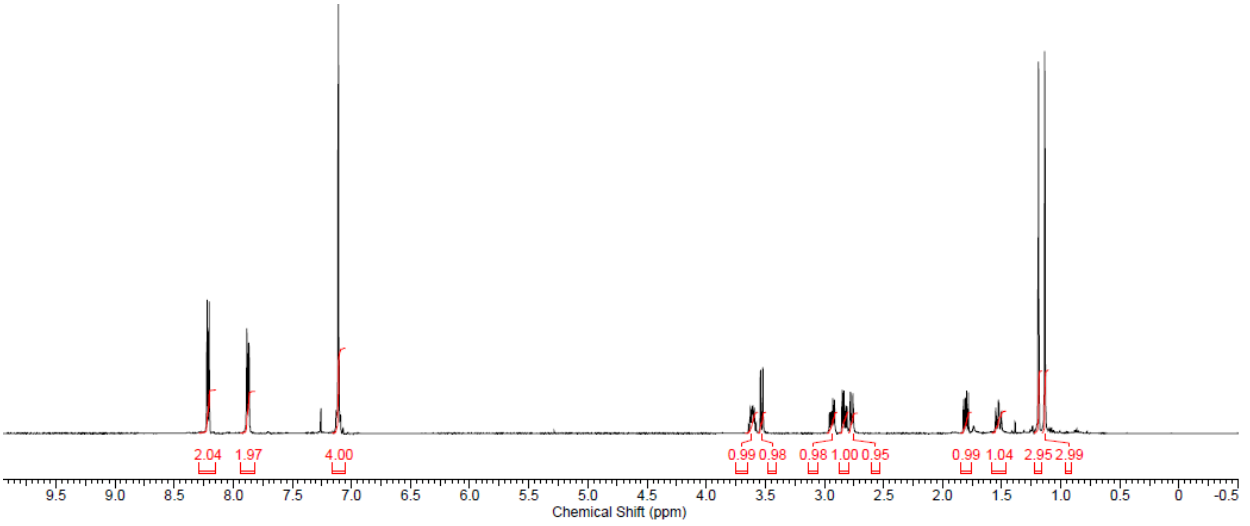
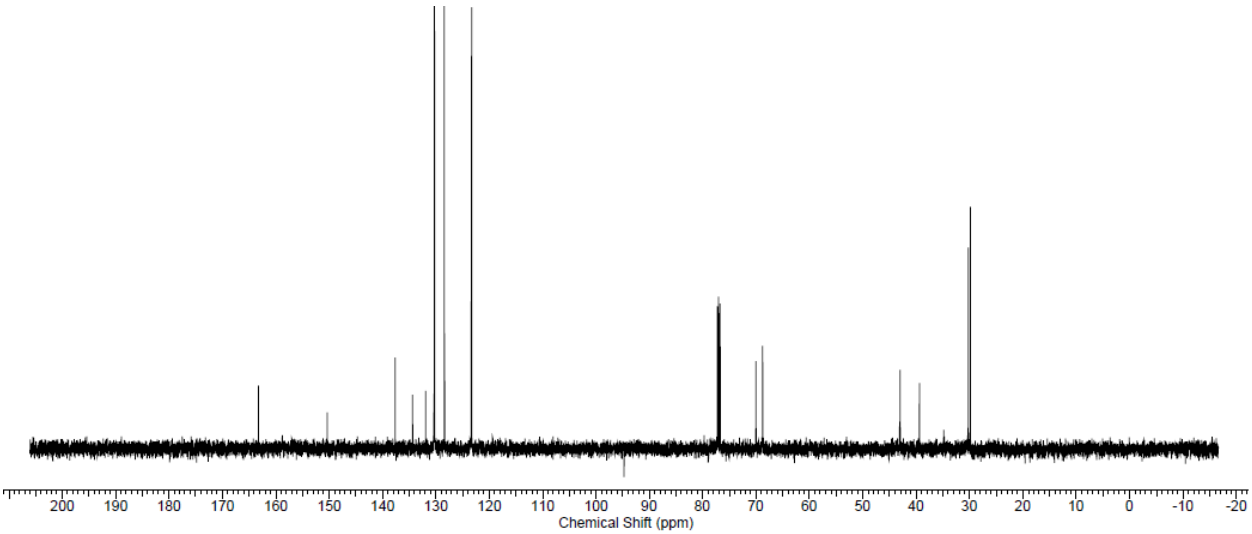
| 2 | 10.131 | BB | 0.3472 | 4678.42334 | 207.41077 | 50.2372 |

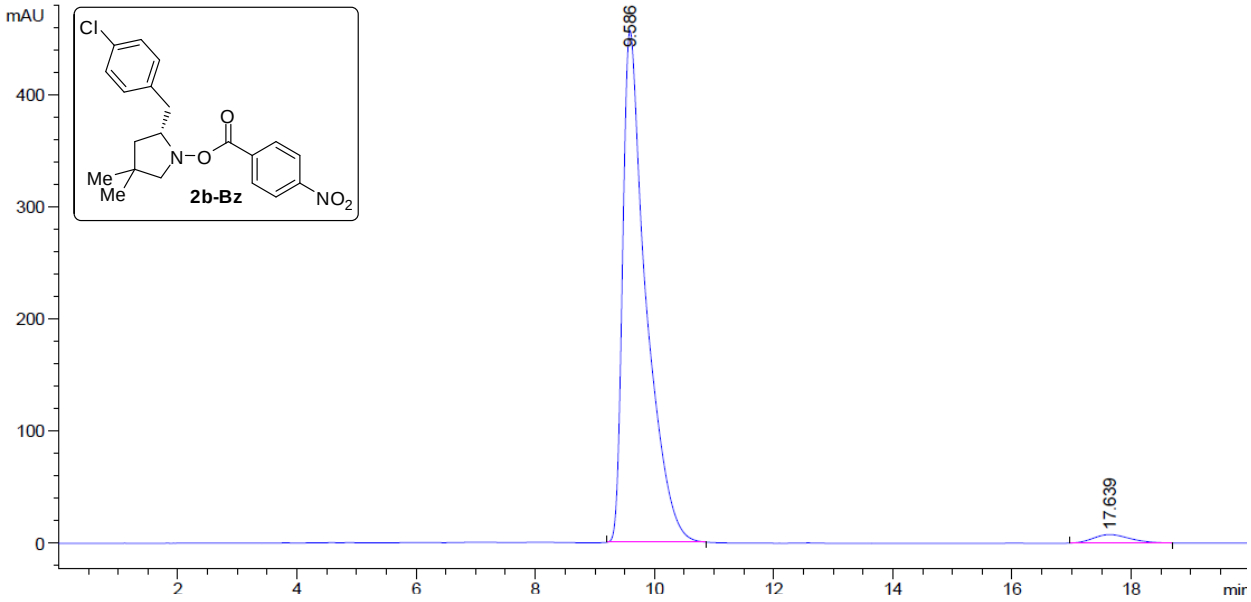



**(*S*)-2-(4-chlorobenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (2b-Bz):** According to the general procedure (method B), hydroxylamine **1b** (0.20 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **2b-Bz** (67.5 mg, 87% yield) as a clear oil. $[\alpha]_D^{25}$=25.1 º (c=0.46, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.21 (d, *J* = 8.8 Hz, 2 H), 7.88 (d, *J* = 8.3 Hz, 2 H), 7.15 - 7.08 (m, 4 H), 3.61 (qd, *J* = 6.9, 10.6 Hz, 1 H), 3.53 (d, *J* = 10.3 Hz, 1 H), 2.93 (dd, *J* = 6.8, 13.7 Hz, 1 H), 2.83 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.77 (d, *J* = 10.3 Hz, 1 H), 1.80 (dd, *J* = 7.6, 12.9 Hz, 1 H), 1.53 (m, 1 H), 1.19 (s, 3 H), 1.16 - 1.12 (m, 3 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.2, 150.4, 137.6, 134.3, 131.9, 130.3, 130.2, 128.4, 123.3, 70.0, 68.8, 43.1, 39.4, 34.8, 30.3, 29.9; FTIR (neat, $cm^{-1}$): 3111 (w), 2959 (m), 2929 (m), 2868 (m), 1742 (s), 1607 (m), 1526 (s), 1492 (m), 1259 (s); LRMS $[M+H]^+$ calculated for $C_{20}H_{22}ClN_2O_4$: 389.12, found: 389.1



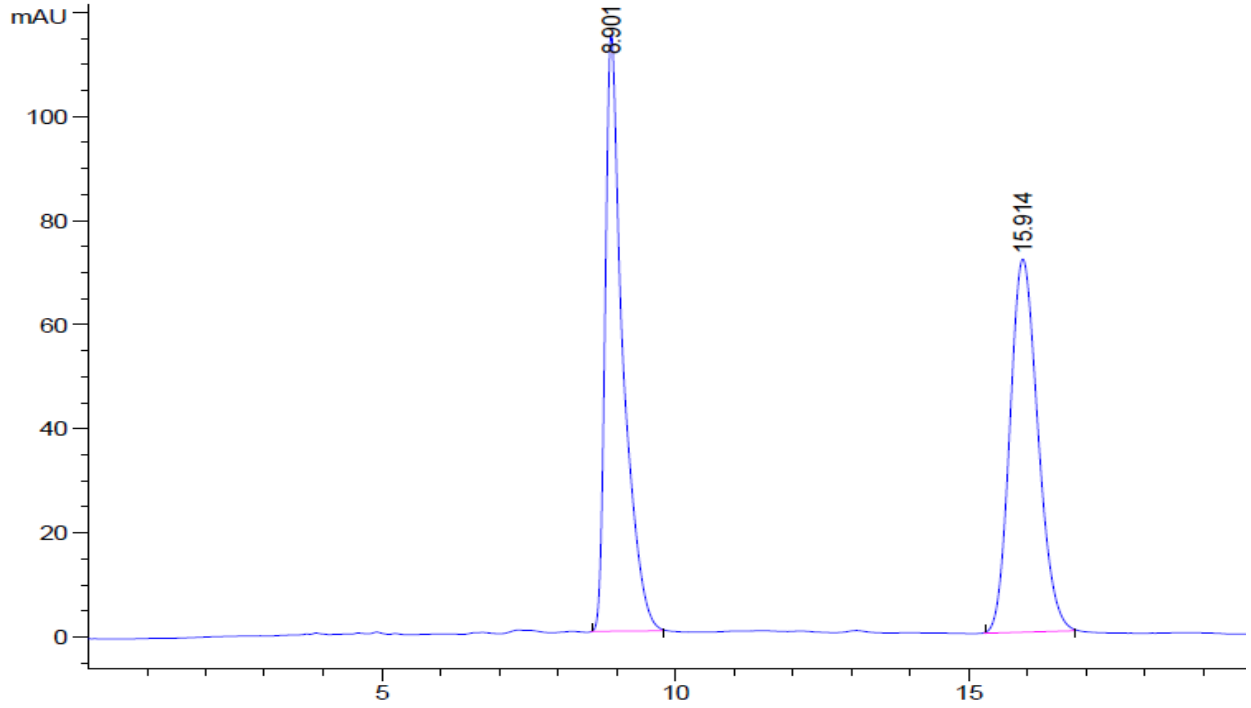



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm), 95% ee

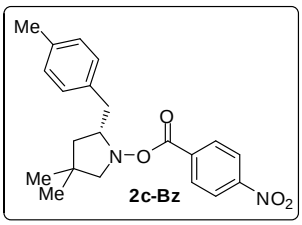



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.586 | BB | 0.3893 | 1.24366e4 | 457.25961 | 97.4471 |
| 2 | 17.639 | BB | 0.6123 | 325.81738 | 7.59805 | 2.5529 |

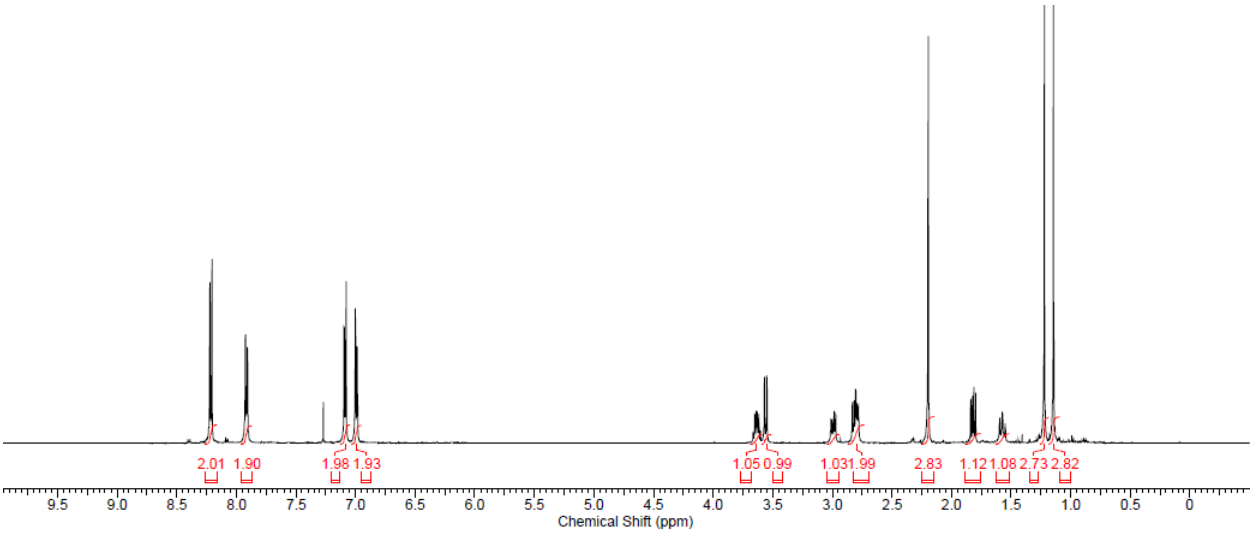
**Racemic Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm)

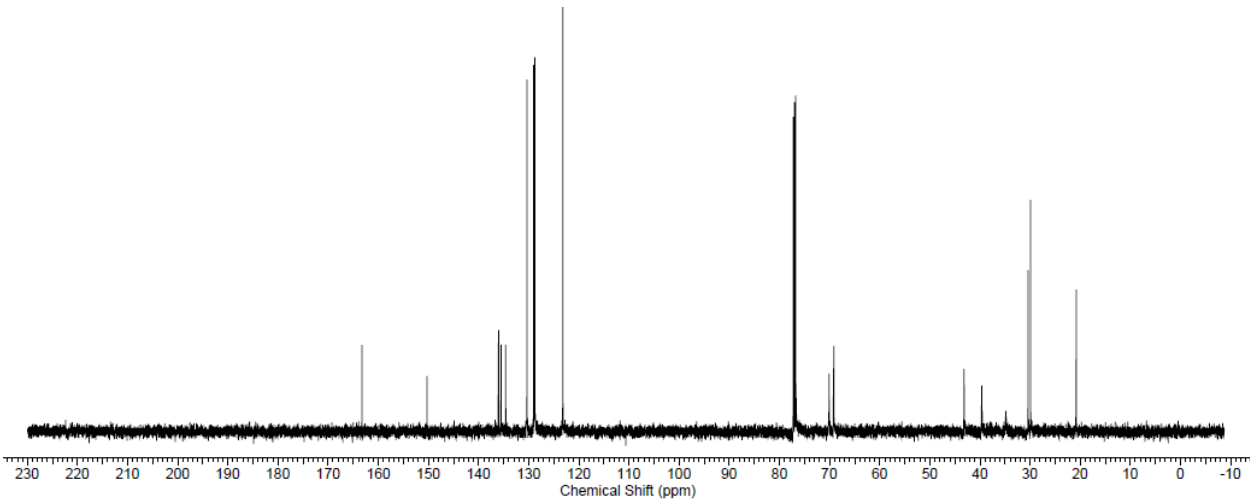



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.901 | BB | 0.3018 | 2418.20386 | 114.75539 | 50.3493 |
| 2 | 15.914 | BB | 0.5180 | 2384.64648 | 71.71127 | 49.6507 |

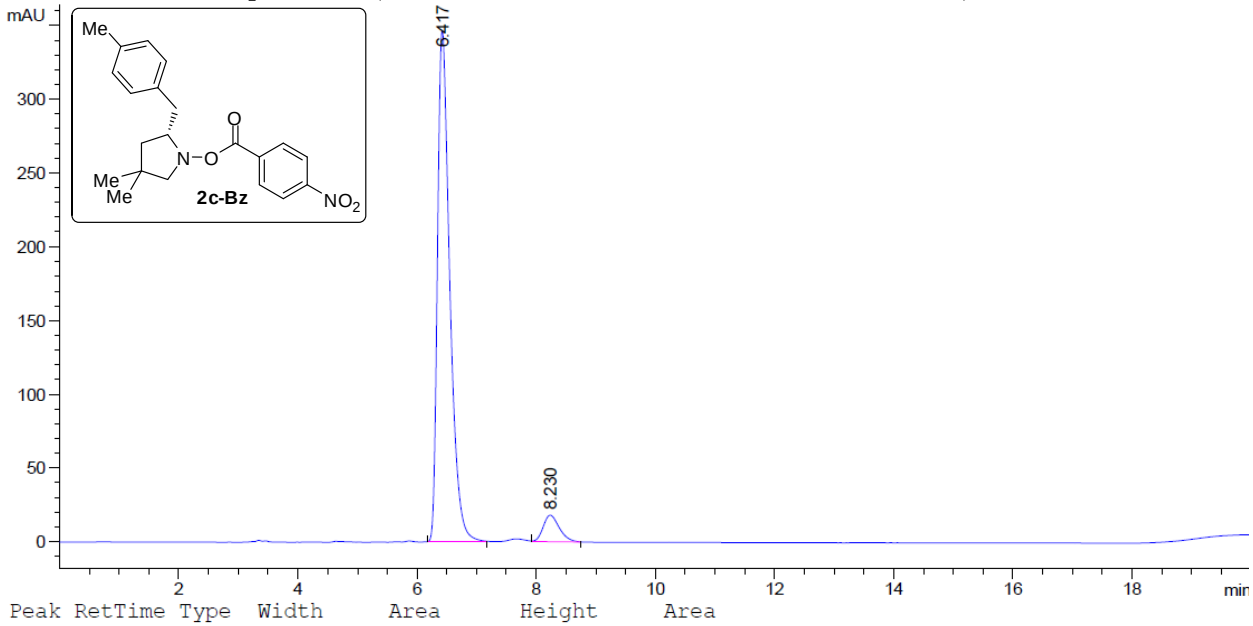



**(*S*)-4,4-dimethyl-2-(4-methylbenzyl)pyrrolidin-1-yl 4-nitrobenzoate (2c-Bz):** According to the general procedure (method C), hydroxylamine **1c** (0.19 mmol) was reacted for 36 h to give the desired *O*-benzoylated hydroxylamine **2c-Bz** (59.1 mg, 84% yield) as a clear oil. $[\alpha]_D^{24}$ =23.3 ° (c=0.84, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.21 (d, *J* = 9.2 Hz, 2 H), 7.91 (d, *J* = 8.7 Hz, 2 H), 7.09 (d, *J* = 8.2 Hz, 2 H), 6.99 (d, *J* = 7.8 Hz, 2 H), 3.63 (qd, *J* = 7.0, 10.5 Hz, 1 H), 3.56 (d, *J* = 10.5 Hz, 1 H), 2.99 (dd, *J* = 6.4, 13.7 Hz, 1 H), 2.87 - 2.74 (m, 2 H), 2.20 (s, 3 H), 1.82 (dd, *J* = 7.3, 12.8 Hz, 1 H), 1.64 - 1.51 (m, 1 H), 1.25 (s, 3 H), 1.15 (s, 3 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.3, 150.3, 136.0, 135.5, 134.6, 130.4, 129.0, 128.8, 123.2, 70.1, 69.2, 43.2, 39.6, 34.8, 30.4, 29.9, 20.8; FTIR (neat, $cm^{-1}$): 3111 (w), 2957 (m), 2867 (m), 1742 (s), 1607 (m), 1526 (s), 1451 (m), 1347 (s), 1258 (s); LRMS $[M+H]^+$ calculated for $C_{21}H_{24}N_2O_4$: 369.17, found: 369.1



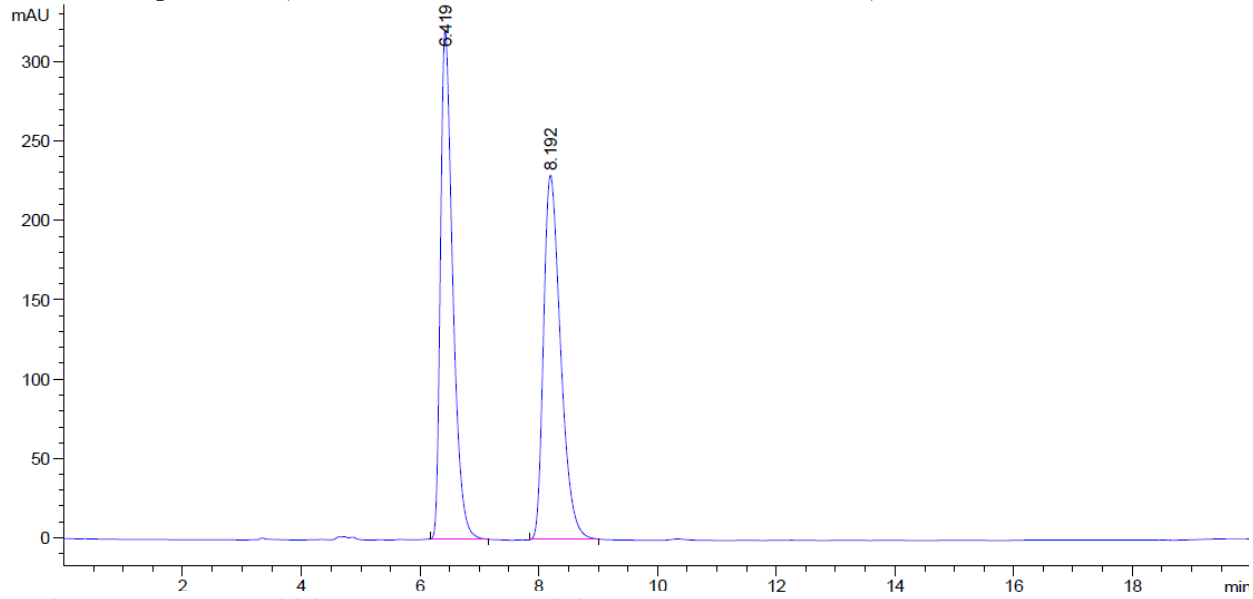



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 230 nm), 87% ee

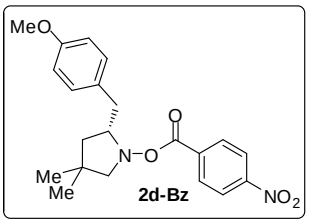



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.417 | BB | 0.2151 | 4969.62256 | 346.98651 | 93.5218 |
| 2 | 8.230 | VB | 0.2874 | 344.24289 | 18.13935 | 6.4782 |

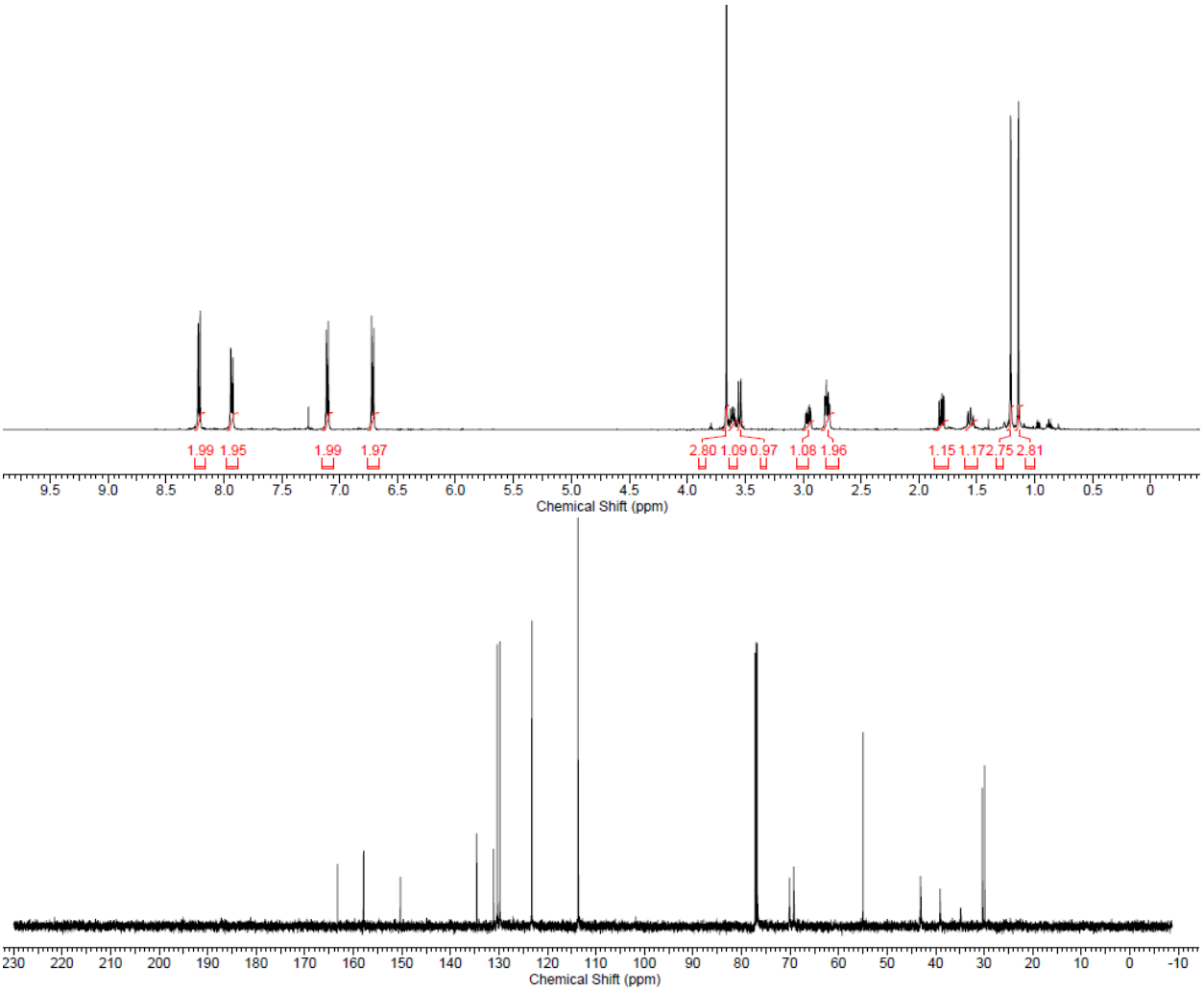
**Racemic Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 230 nm)



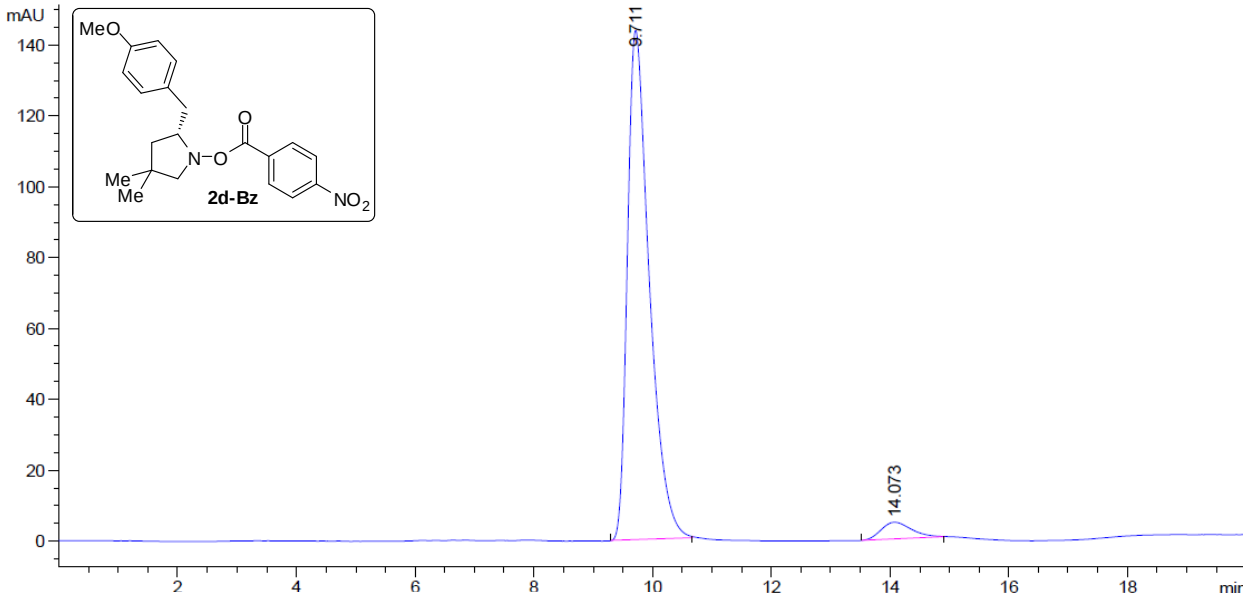

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.419 | BB | 0.2176 | 4610.44385 | 320.88708 | 50.0563 |
| 2 | 8.192 | BB | 0.3097 | 4600.07910 | 229.61908 | 49.9437 |




**(*S*)-2-(4-methoxybenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (2d-Bz):** According to the general procedure (method C), hydroxylamine **1d** (0.18 mmol) was reacted for 96 h to give the desired *O*-benzoylated hydroxylamine **2d-Bz** (63.5 mg, 96% yield) as a clear oil. $[\alpha]_D^{25}$=26.5 º (c=0.92, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.21 (d, *J* = 8.7 Hz, 2 H), 7.93 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 6.71 (d, *J* = 8.7 Hz, 2 H), 3.66 (s, 3 H), 3.61 (qd, *J* = 6.9, 10.5 Hz, 1 H), 3.55 (d, *J* = 10.1 Hz, 1 H), 2.96 (dd, *J* = 6.4, 13.7 Hz, 1 H), 2.83 - 2.74 (m, 2 H), 1.81 (dd, *J* = 7.3, 12.8 Hz, 1 H), 1.61 - 1.51 (m, 1 H), 1.21 (s, 3 H), 1.14 (s, 3 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.3, 157.9, 150.3, 134.6, 131.1, 130.3, 129.8, 123.2, 113.7, 70.1, 69.2, 55.0, 43.1, 39.1, 34.8, 30.4, 29.9; FTIR (neat, $cm^{-1}$): 3112 (w), 2958 (m), 2868 (m), 1742 (s), 1610 (m), 1527 (s), 1513 (s), 1348 (m), 1249 (s); LRMS $[M+H]^+$ calculated for $C_{21}H_{24}N_2O_5$: 385.17, found: 385.1

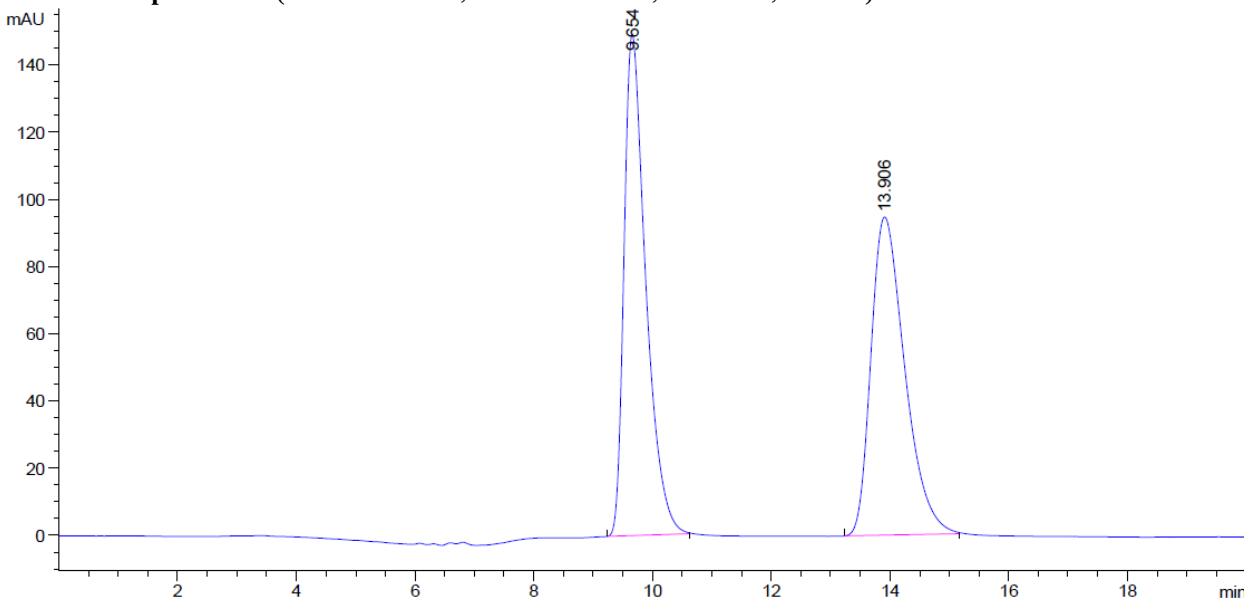


**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm), 91% ee

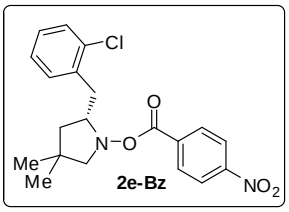



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.711 | BB | 0.3832 | 3691.09106 | 143.94705 | 95.5780 |
| 2 | 14.073 | BB | 0.5288 | 170.77342 | 4.73481 | 4.4220 |

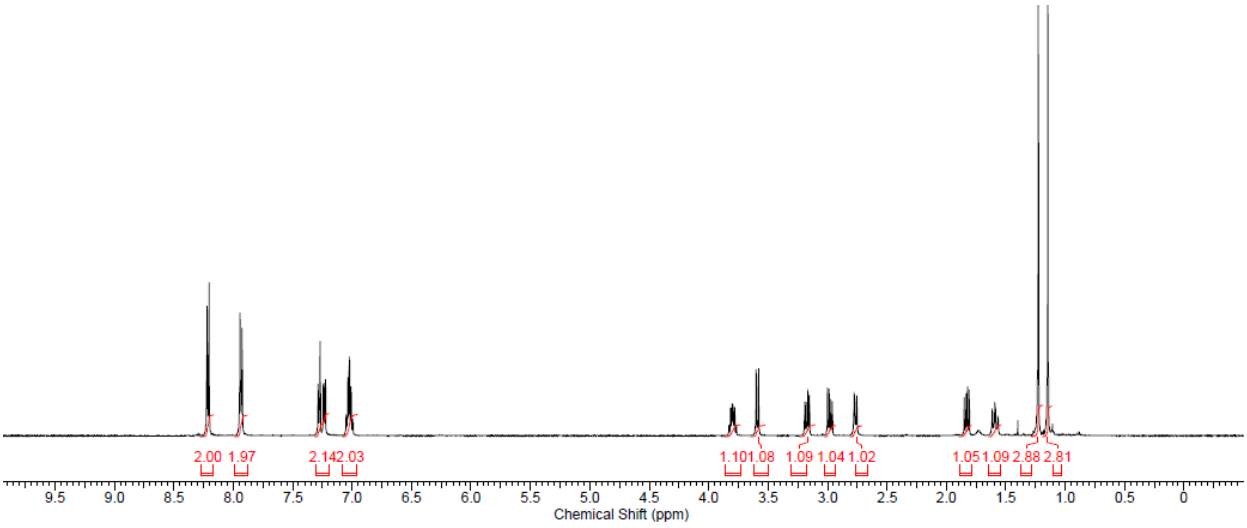
**Racemic Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm)

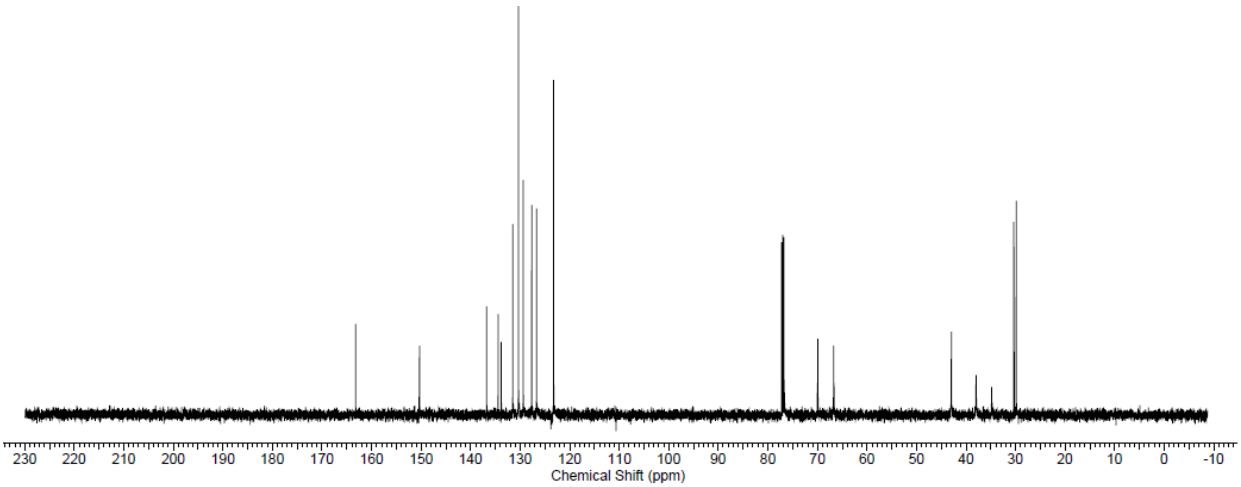



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.654 | BB | 0.3811 | 3800.89209 | 149.25887 | 50.3667 |
| 2 | 13.906 | BB | 0.6076 | 3745.55176 | 94.66926 | 49.6333 |

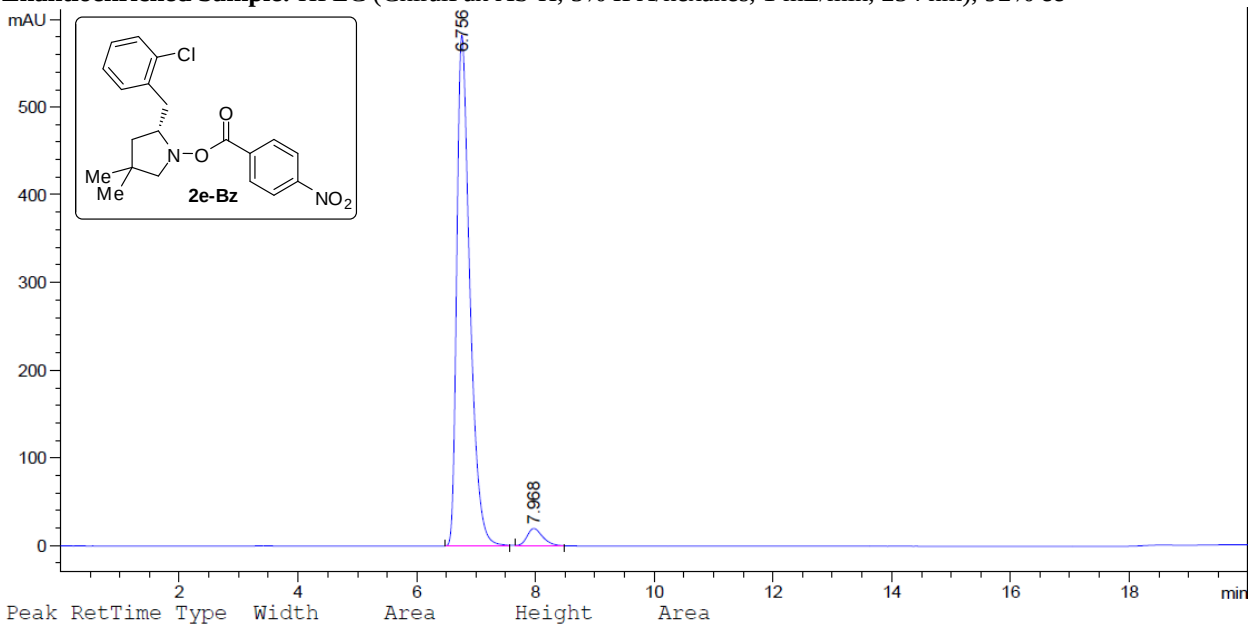



**(*S*)-2-(2-chlorobenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (2e-Bz):** According to the general procedure (method B), hydroxylamine **1e** (0.18 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **2e-Bz** (64.0 mg, 91% yield) as a clear oil. $[\alpha]_D^{25}$=3.2 º (c=0.67, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.21 (d, *J* = 8.7 Hz, 2 H), 7.93 (d, *J* = 8.7 Hz, 2 H), 7.32 - 7.20 (m, 2 H), 7.02 (dquin, *J* = 1.6, 7.0 Hz, 2 H), 3.80 (qd, *J* = 6.9, 10.4 Hz, 1 H), 3.59 (d, *J* = 10.1 Hz, 1 H), 3.17 (dd, *J* = 6.6, 13.5 Hz, 1 H), 2.98 (dd, *J* = 6.6, 13.5 Hz, 1 H), 2.76 (d, *J* = 10.1 Hz, 1 H), 1.83 (dd, *J* = 7.3, 12.8 Hz, 1 H), 1.59 (m, 1 H), 1.27 - 1.20 (m, 1 H), 1.15 (s, 1 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.2, 150.3, 136.8, 134.5, 133.8, 131.5, 130.3, 129.4, 127.7, 126.7, 123.3, 70.0, 66.7, 43.0, 38.0, 34.8, 30.4, 29.9; FTIR (neat, $cm^{-1}$): 3111 (w), 2959 (m), 2868 (m), 1743 (s), 1607 (m), 1527 (s), 1474 (m), 1444 (m), 1348 (s), 1259 (s); LRMS $[M+H]^+$ calculated for $C_{20}H_{22}ClN_2O_4$: 389.12, found: 389.1



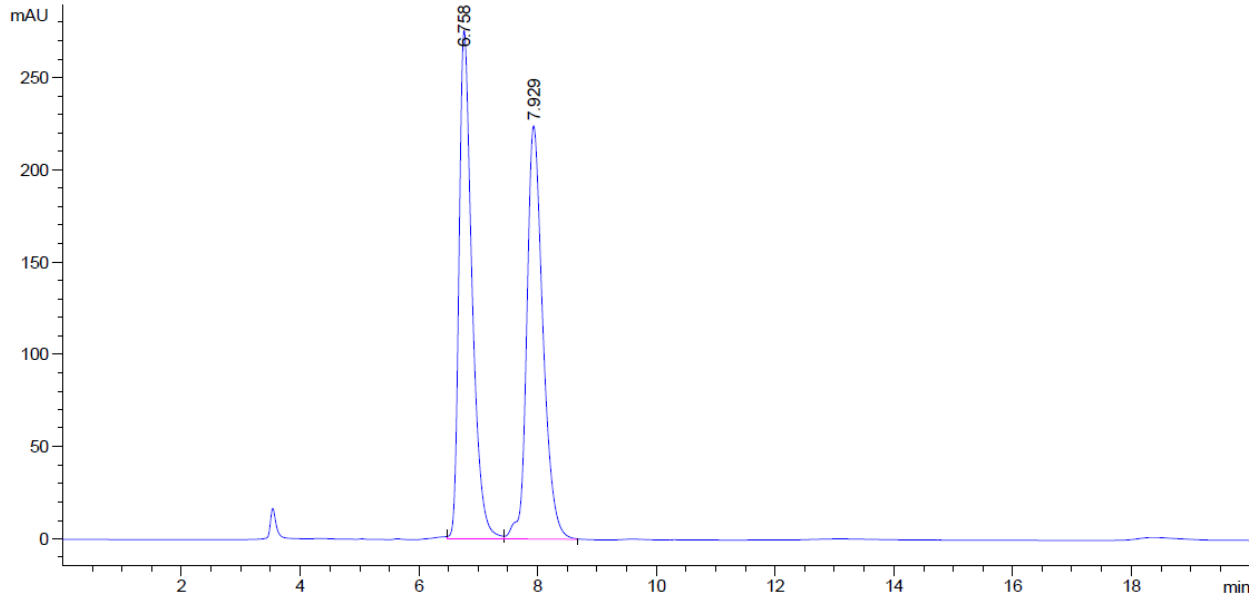



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm), 92% ee

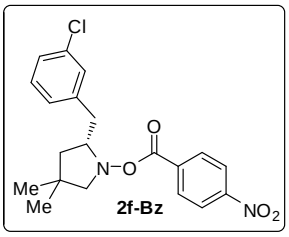



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.756 | BB | 0.2306 | 8916.22363 | 582.43860 | 96.0173 |
| 2 | 7.968 | BB | 0.2806 | 369.83365 | 19.91801 | 3.9827 |

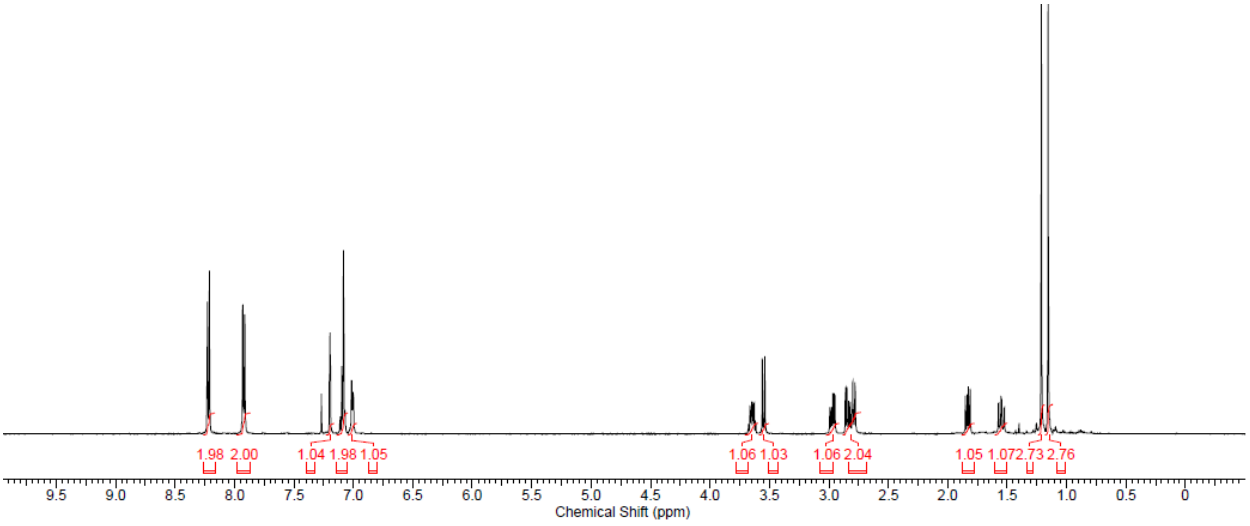
**Racemic Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm)

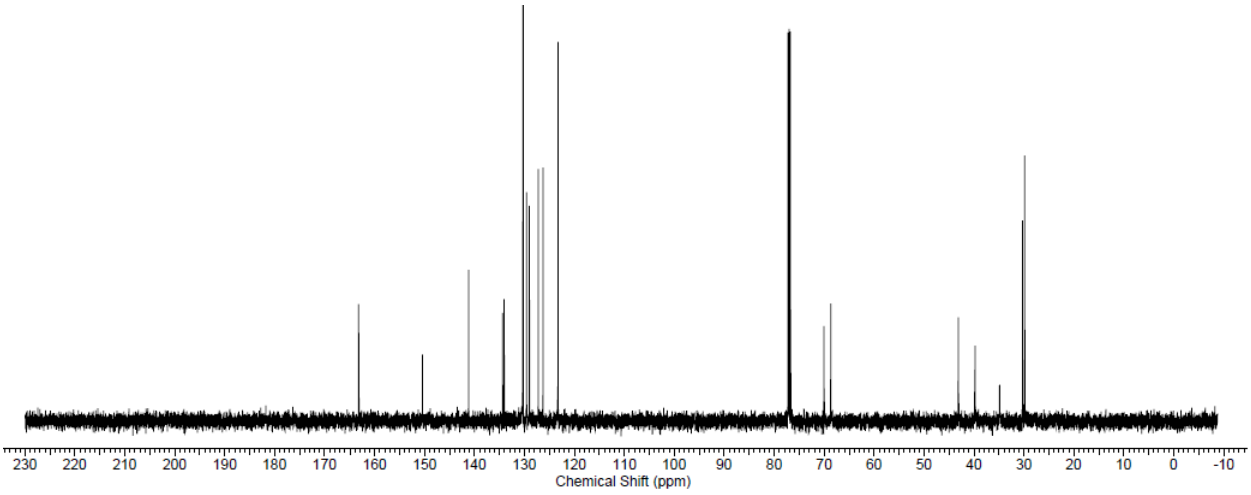



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.758 | BV | 0.2278 | 4201.37793 | 275.71591 | 49.8514 |
| 2 | 7.929 | VB | 0.2862 | 4226.42139 | 223.97264 | 50.1486 |

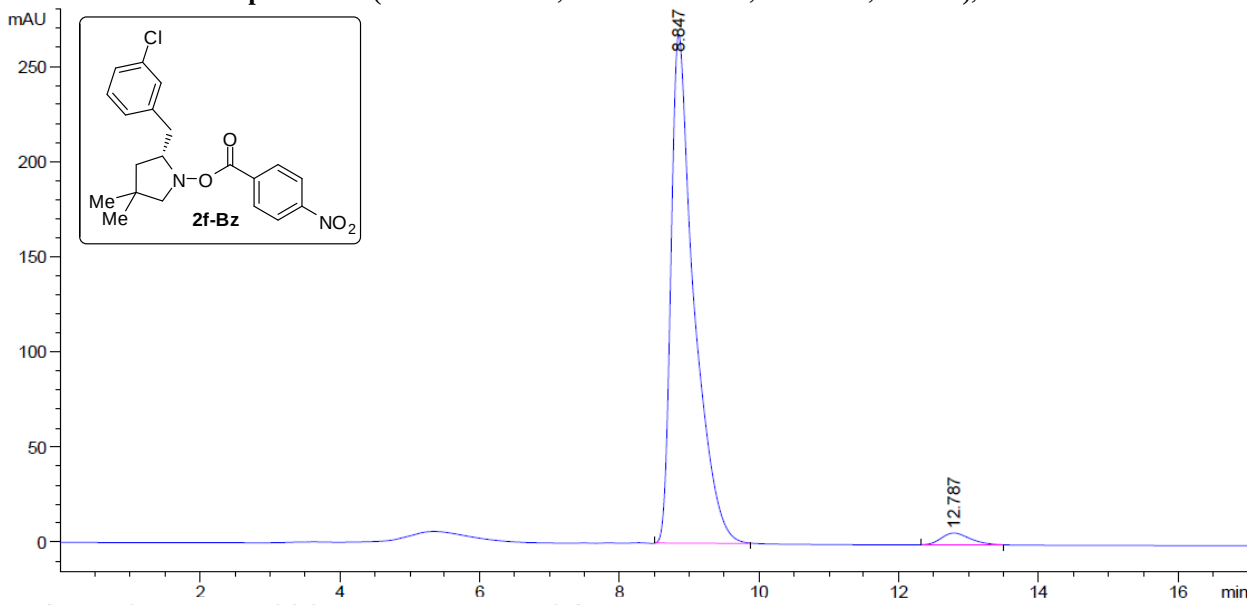



**(*S*)-2-(3-chlorobenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (2f-Bz):** According to the general procedure (method B), hydroxylamine **1f** (0.22 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **2f-Bz** (74.3 mg, 87% yield) as a clear oil. $[\alpha]_D^{25}$=14.4 º (c=0.65, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.22 (d, *J* = 8.2 Hz, 2 H), 7.92 (d, *J* = 8.7 Hz, 2 H), 7.20 (s, 1 H), 7.13 - 7.06 (m, 2 H), 7.03 - 6.98 (m, 1 H), 3.65 (qd, *J* = 7.1, 10.4 Hz, 1 H), 3.55 (d, *J* = 10.1 Hz, 1 H), 2.97 (dd, *J* = 6.6, 13.5 Hz, 1 H), 2.84 (dd, *J* = 6.4, 13.7 Hz, 1 H), 2.79 (d, *J* = 10.1 Hz, 1 H), 1.83 (dd, *J* = 7.8, 12.8 Hz, 1 H), 1.60 - 1.50 (m, 1 H), 1.21 (s, 3 H), 1.16 (s, 3 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.2, 150.4, 141.2, 134.4, 134.1, 130.3, 129.6, 129.0, 127.2, 126.3, 123.3, 70.2, 68.7, 43.1, 39.8, 34.9, 30.3, 29.9; FTIR (neat, $cm^{-1}$): 2958 (m), 2868 (m), 1745 (s) 1600 (m), 1528 (s), 1477 (w), 1349 (m), 1261 (s); LRMS $[M+H]^+$ calculated for $C_{20}H_{22}ClN_2O_4$: 389.12, found: 389.1



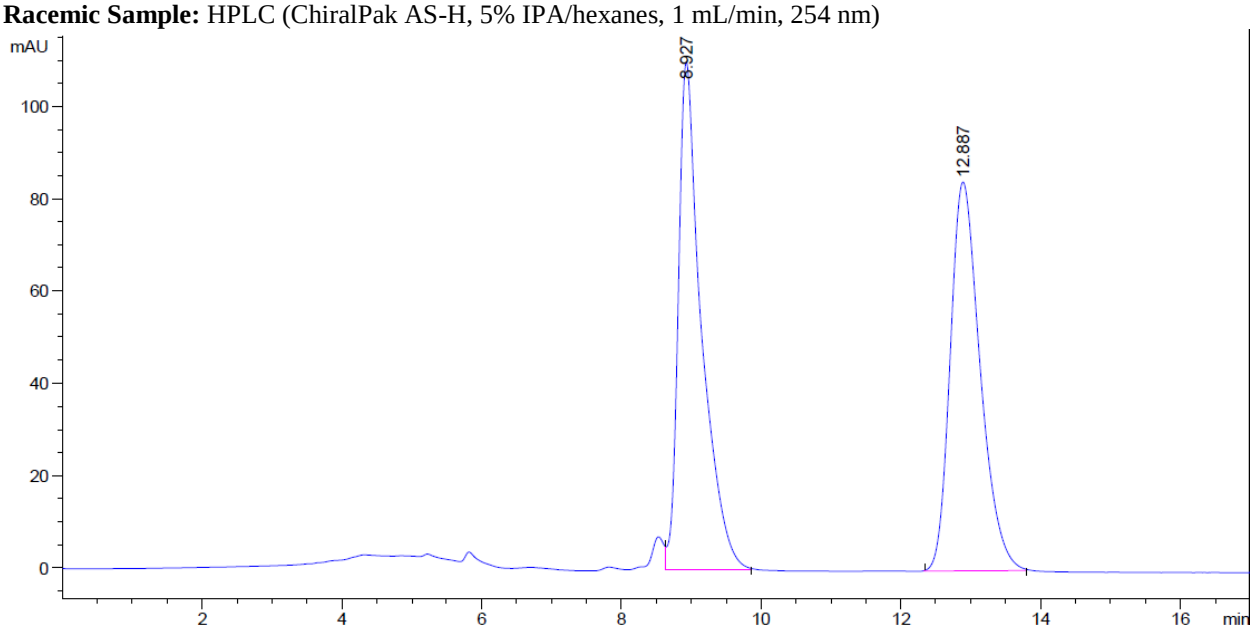



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm), 94% ee

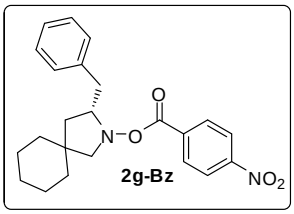



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.847 | BB | 0.3284 | 6107.02979 | 267.48981 | 97.1415 |
| 2 | 12.787 | BB | 0.4307 | 179.70747 | 6.22684 | 2.8585 |

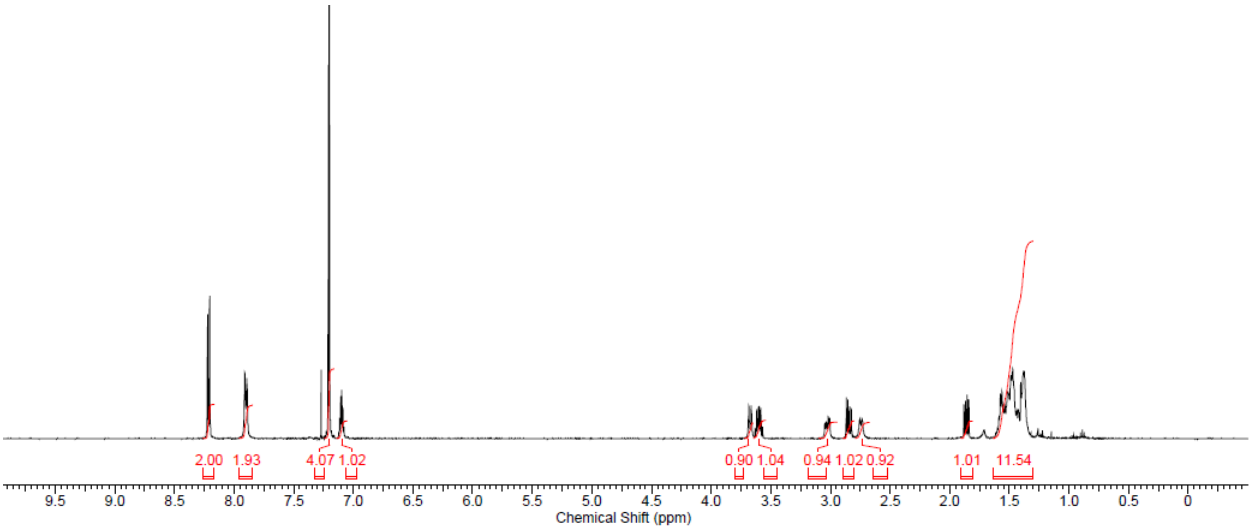
**Racemic Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm)

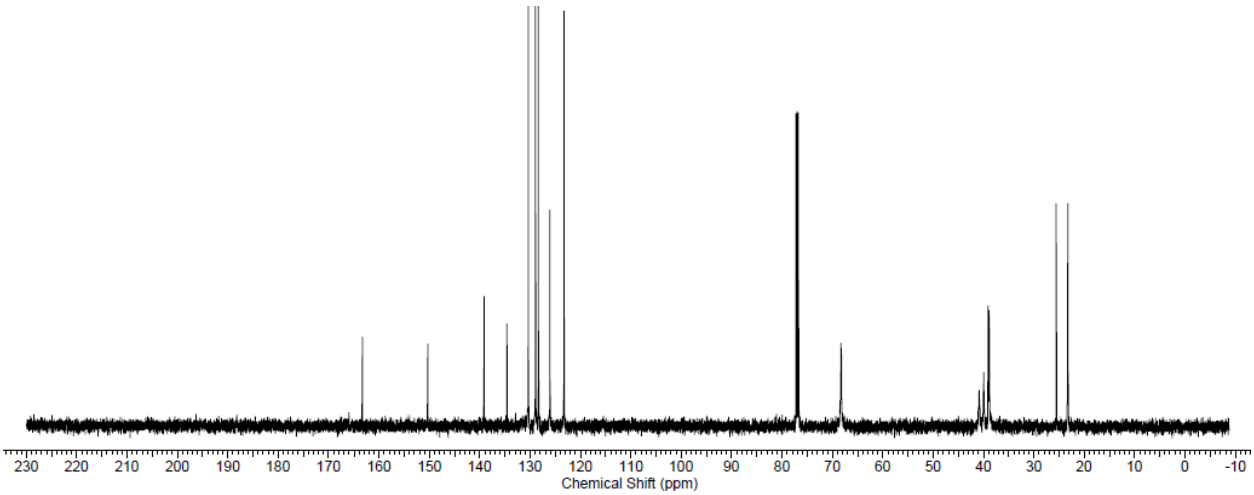



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.927 | VB | 0.3288 | 2535.49072 | 110.03610 | 50.2402 |
| 2 | 12.887 | BB | 0.4536 | 2511.24512 | 84.28941 | 49.7598 |

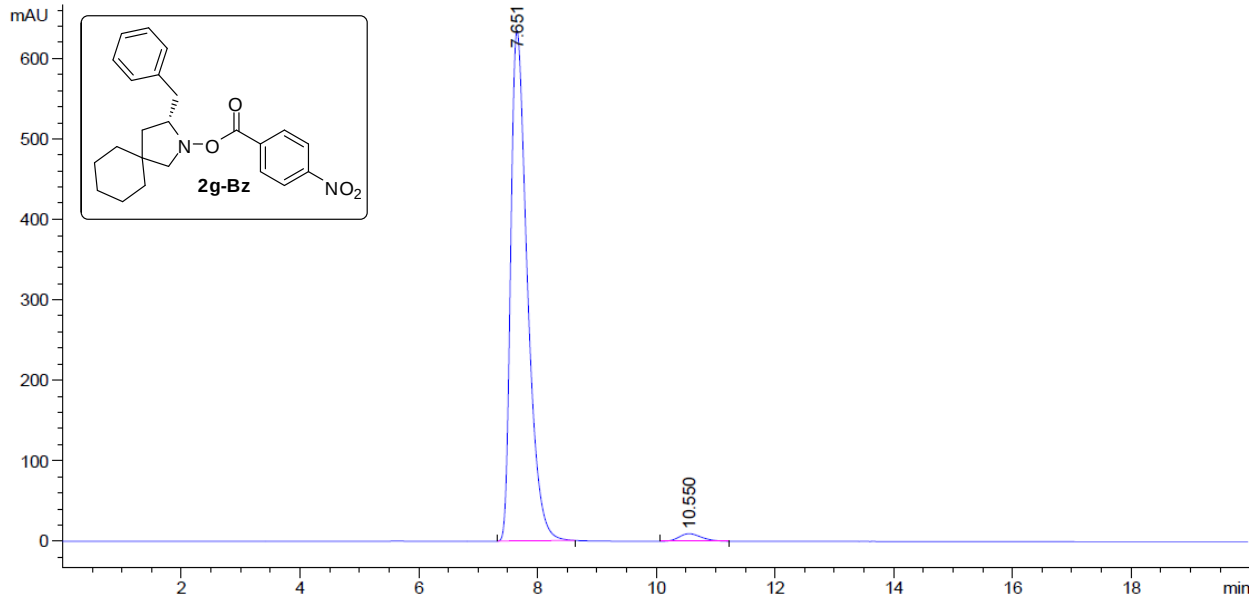



**(*S*)-3-benzyl-2-azaspiro[4.5]decan-2-yl 4-nitrobenzoate (2g-Bz):** According to the general procedure (method B), hydroxylamine **1g** (0.20 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **2g-Bz** (64.8 mg, 82% yield) as a clear oil. $[\alpha]_D^{25}$=25.9 º (c=0.61, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.21 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 4.4 Hz, 4 H), 7.13 - 7.06 (m, 1 H), 3.67 (d, *J* = 10.3 Hz, 1 H), 3.60 (qd, *J* = 6.8, 10.7 Hz, 1 H), 3.03 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.85 (dd, *J* = 6.8, 13.7 Hz, 1 H), 2.74 (d, *J* = 9.8 Hz, 1 H), 1.86 (dd, *J* = 7.1, 12.9 Hz, 1 H), 1.64 - 1.31 (m, 10 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.3, 150.3, 139.2, 134.6, 130.4, 128.9, 128.4, 126.1, 123.3, 68.3, 40.9, 40.0, 39.1, 38.9, 25.6, 23.4, 23.3; FTIR (neat, $cm^{-1}$): 3110 (w), 2926 (s), 2853 (m), 1743 (s), 1606 (m), 1527 (s), 1452 (m), 1319 (m), 1261 (s); LRMS $[M+H]^+$ calculated for $C_{23}H_{26}N_2O_4$: 395.19, found: 395.1



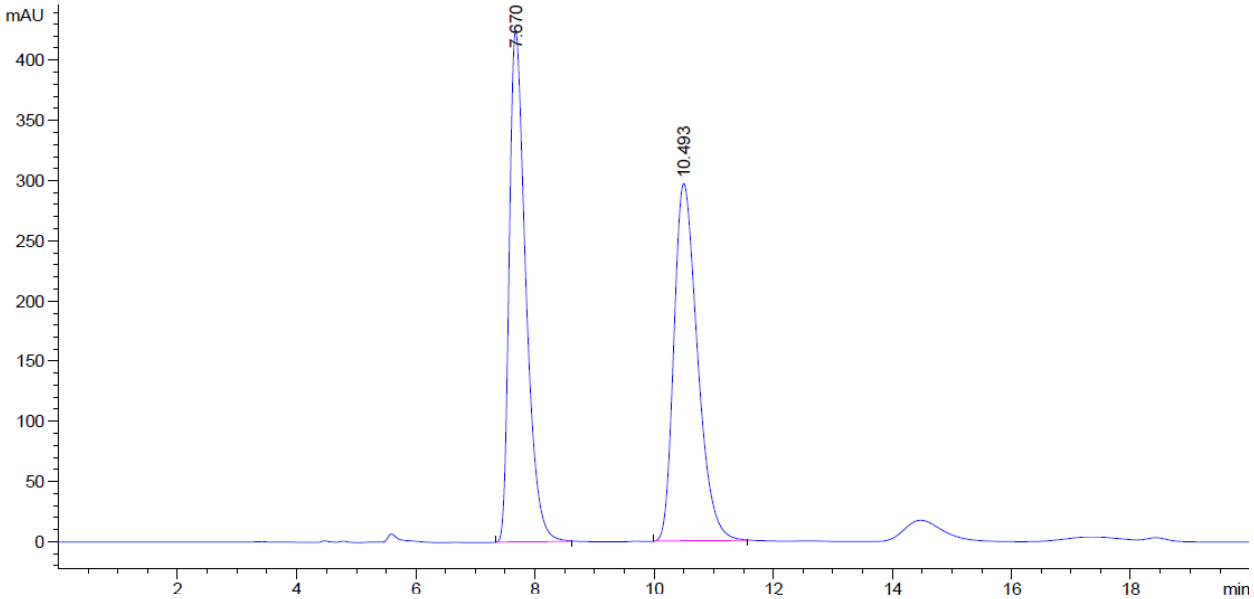



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm), 96% ee

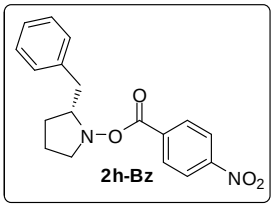



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 7.651 | BB | 0.2947 | 1.23313e4 | 634.61871 | 98.0075 |
| 2 | 10.550 | BB | 0.4049 | 250.69958 | 9.47002 | 1.9925 |

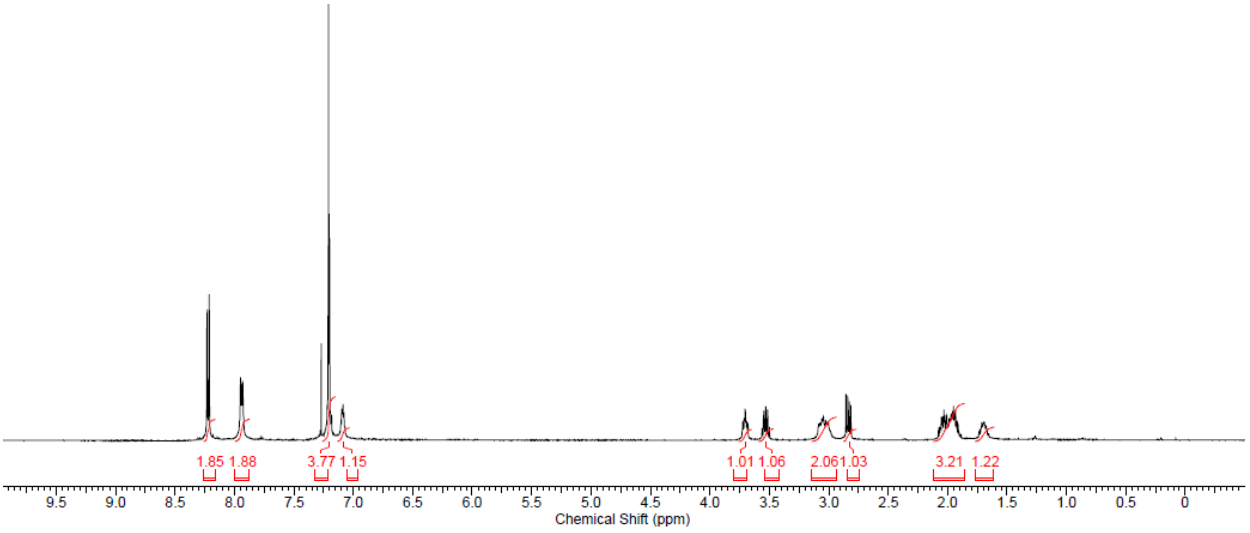
**Racemic Sample:** HPLC (ChiralPak AS-H, 5% IPA/hexanes, 1 mL/min, 254 nm)

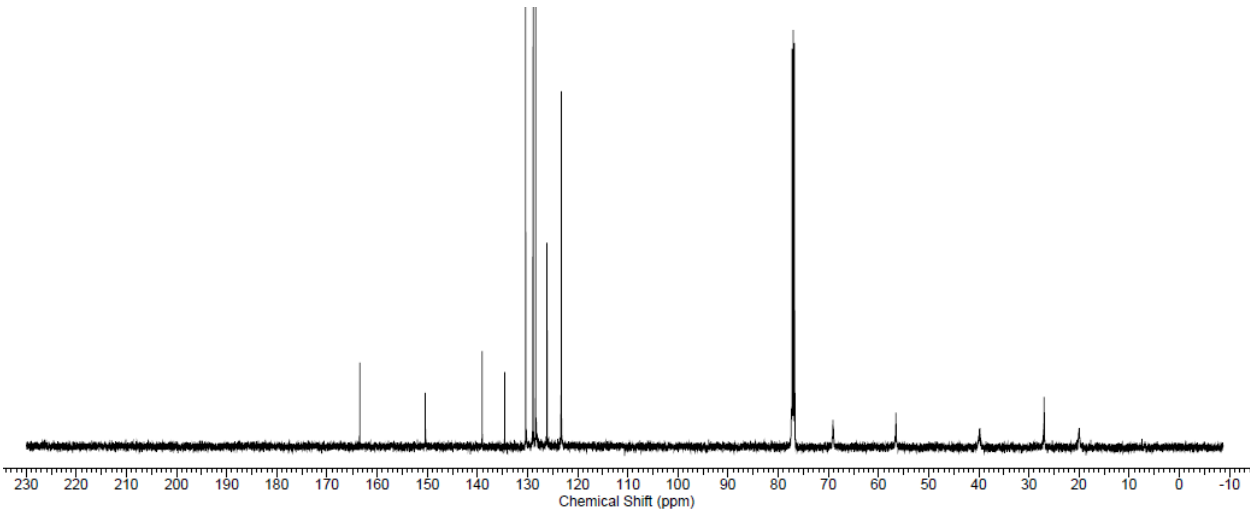



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 7.670 | BB | 0.2932 | 8209.57617 | 425.25714 | 50.1105 |
| 2 | 10.493 | BB | 0.4248 | 8173.38232 | 297.25320 | 49.8895 |

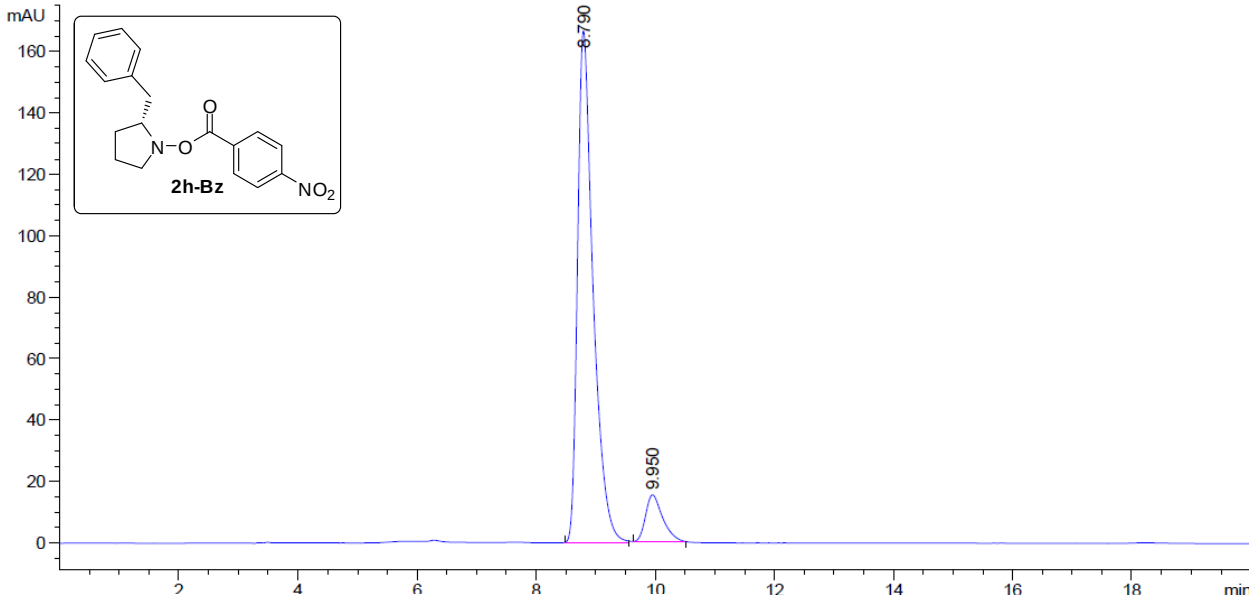



**(*R*)-2-benzylpyrrolidin-1-yl 4-nitrobenzoate (2h-Bz):** According to the general procedure (method D), hydroxylamine **1g** (0.20 mmol) was reacted for 72 h at 30 ºC to give the desired *O*-benzoylated hydroxylamine **2f-Bz** (44.6 mg, 68% yield) as a clear oil. $[\alpha]_D^{25}$=8.7 º (c=0.98, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.22 (d, *J* = 8.7 Hz, 2 H), 7.94 (d, *J* = 8.2 Hz, 2 H), 7.24 - 7.16 (m, 4 H), 7.12 - 7.04 (m, 1 H), 3.77 - 3.65 (m, 1 H), 3.53 (qd, *J* = 7.1, 9.4 Hz, 1 H), 3.14 - 2.96 (m, 2 H), 2.83 (dd, *J* = 7.3, 13.7 Hz, 1 H), 2.14 - 1.86 (m, 3 H), 1.78 - 1.61 (m, 1 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.5, 150.4, 139.1, 134.6, 130.4, 128.9, 128.4, 126.1, 123.3, 69.1, 56.6, 39.8, 27.0, 20.0; FTIR (neat, $cm^{-1}$): 3110 (w), 3028 (w), 2977 (m), 2869 (m), 1741 (s), 1606 (m), 1526 (s), 1496 (m), 1347 (s), 1259 (s); LRMS $[M+H]^+$ calculated for $C_{18}H_{18}N_2O_4$: 327.13, found: 327.1



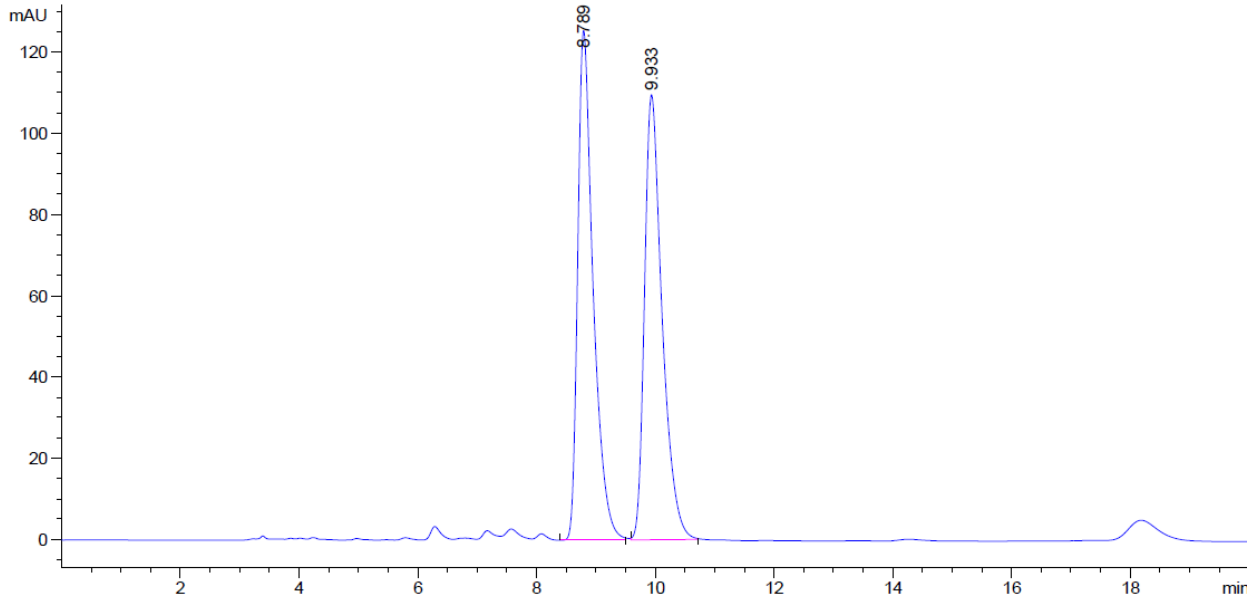



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 10% IPA/hexanes, 1 mL/min, 254 nm), 81% ee

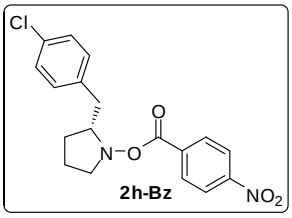



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.790 | BB | 0.2677 | 3024.61475 | 166.71098 | 90.5264 |
| 2 | 9.950 | BB | 0.3023 | 316.52789 | 15.49707 | 9.4736 |

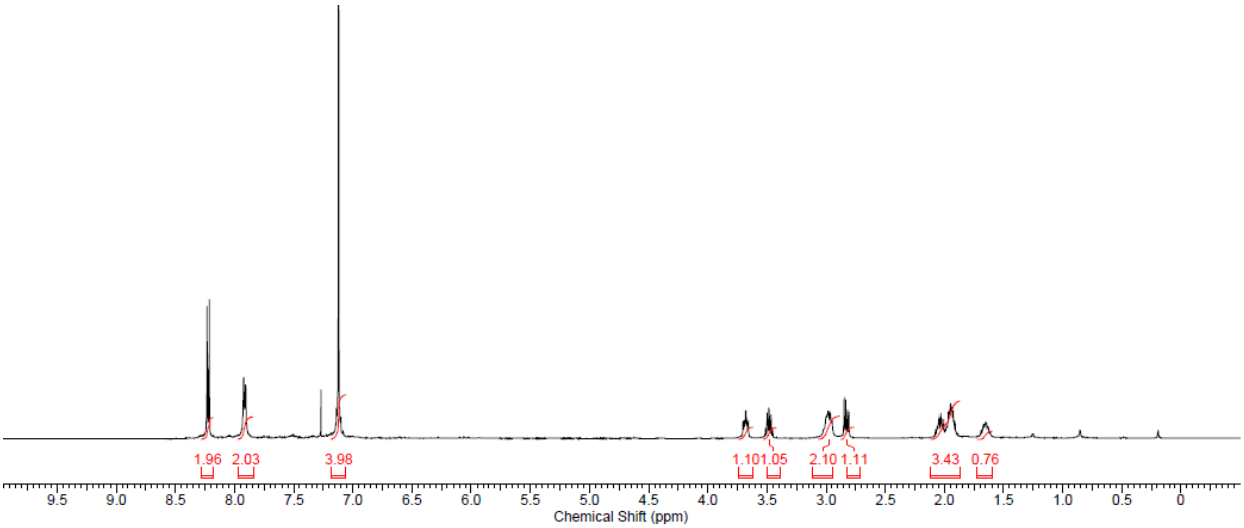
**Racemic Sample:** HPLC (ChiralPak AS-H, 10% IPA/hexanes, 1 mL/min, 254 nm)

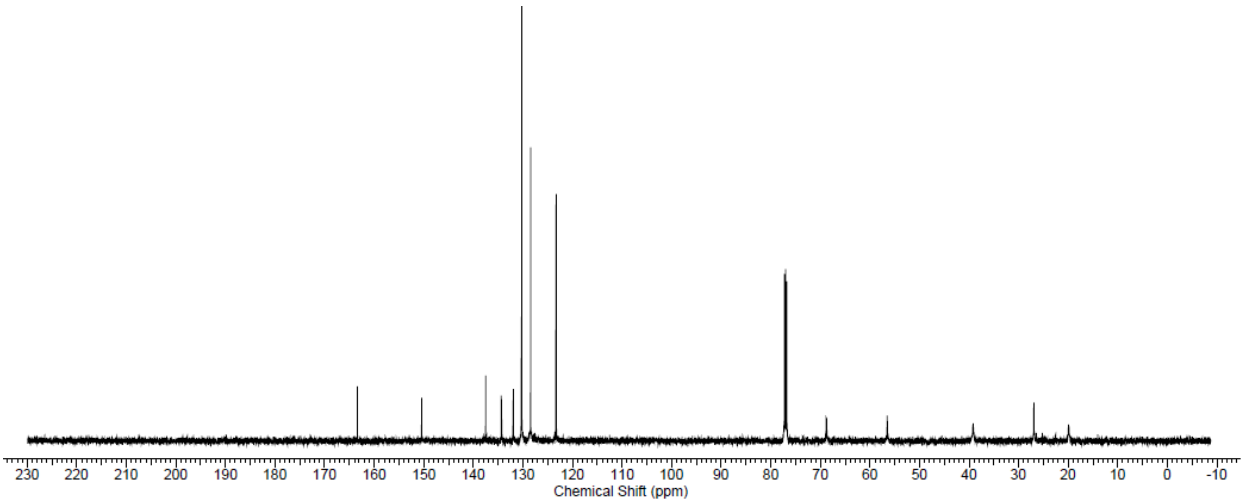



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.789 | VB | 0.2688 | 2265.74194 | 125.42463 | 50.0920 |
| 2 | 9.933 | BB | 0.3085 | 2257.42212 | 109.49364 | 49.9080 |

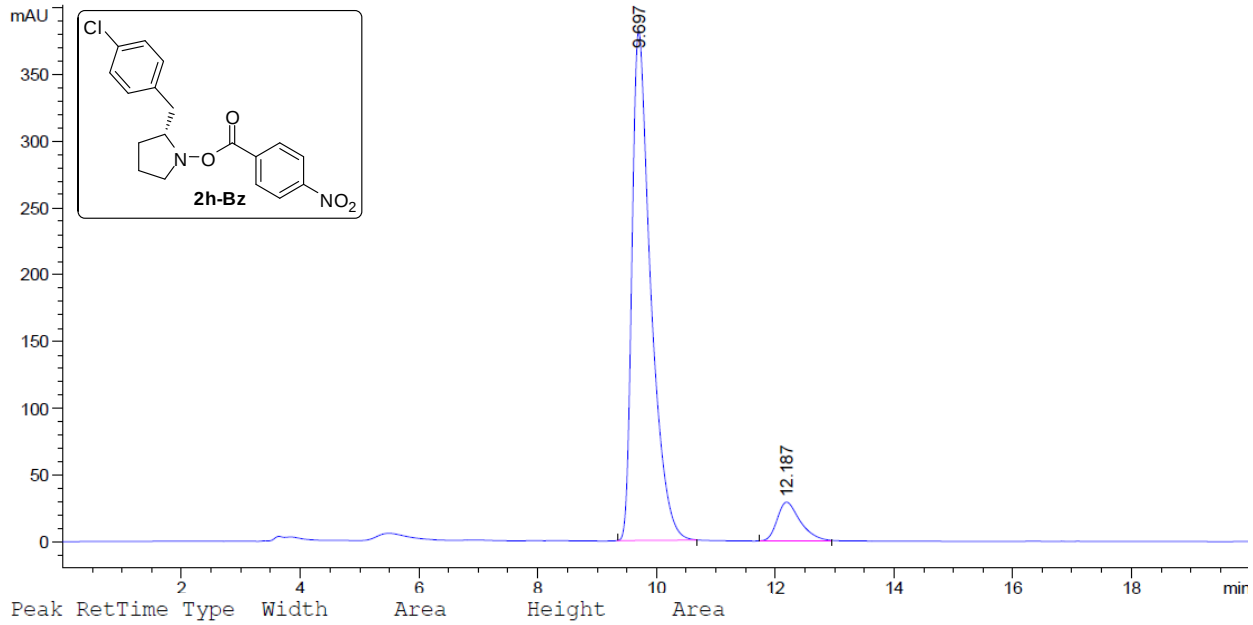



**(*R*)-2-(4-chlorobenzyl)pyrrolidin-1-yl 4-nitrobenzoate (2h-Bz):** According to the general procedure (method D), hydroxylamine **1h** (0.20 mmol) was reacted for 72 h at 30 ºC to give the desired *O*-benzoylated hydroxylamine **2f-Bz** (67.1 mg, 93% yield) as a clear oil. $[\alpha]_D^{25}$=17.0 º (c=1.45, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.22 (d, *J* = 9.2 Hz, 2 H), 7.91 (d, *J* = 8.7 Hz, 2 H), 7.16 - 7.07 (m, 4 H), 3.68 (ddd, *J* = 4.1, 7.1, 10.8 Hz, 1 H), 3.48 (qd, *J* = 7.2, 9.2 Hz, 1 H), 3.09 - 2.90 (m, 2 H), 2.83 (dd, *J* = 6.4, 13.7 Hz, 1 H), 2.11 - 1.87 (m, 3 H), 1.73 - 1.57 (m, 1 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.4, 150.4, 137.5, 134.3, 132.0, 130.3, 128.4, 123.3, 68.8, 56.5, 39.2, 26.9, 19.9; FTIR (neat, $cm^{-1}$): 3019 (m), 2955 (m), 2864 (w), 1742 (s), 1607 (m), 1529 (s), 1492 (m), 1348 (m), 1261 (s), 1216 (s); LRMS $[M+H]^+$ calculated for $C_{18}H_{18}ClN_2O_4$: 361.09, found: 361.0



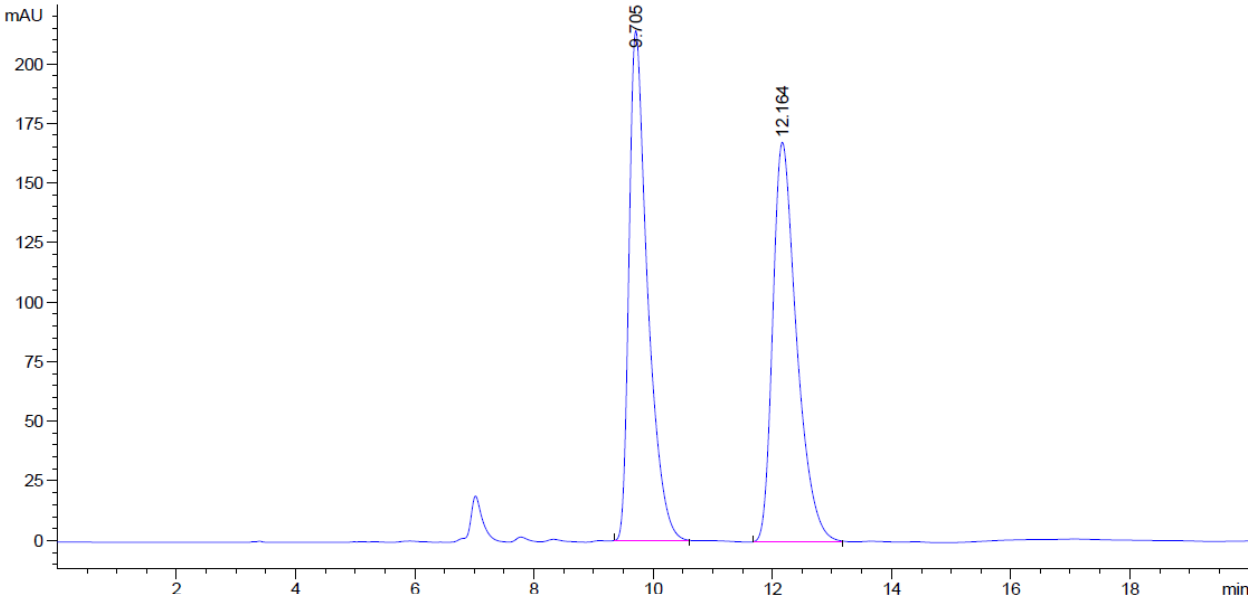



**Enantioenriched Sample:** HPLC (ChiralPak AS-H, 10% IPA/hexanes, 1 mL/min, 254 nm), 83% ee

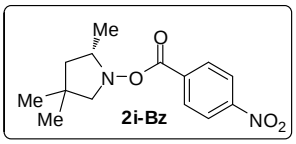



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.697 | BB | 0.3241 | 8374.29688 | 381.51385 | 91.4715 |
| 2 | 12.187 | BB | 0.4044 | 780.79419 | 28.97688 | 8.5285 |

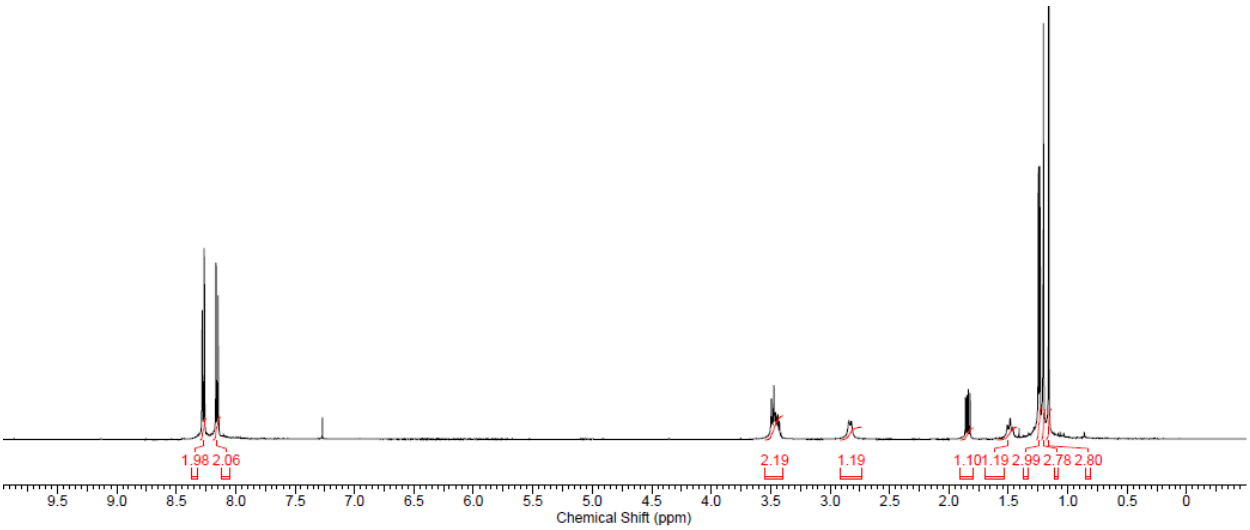
**Racemic Sample:** HPLC (ChiralPak AS-H, 10% IPA/hexanes, 1 mL/min, 254 nm)

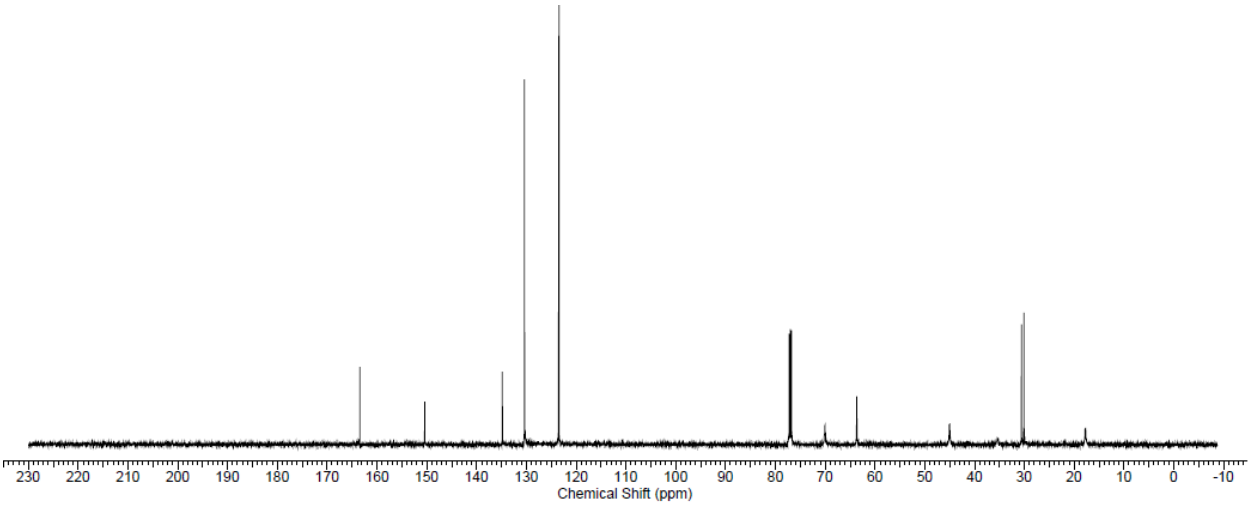



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.705 | BB | 0.3191 | 4643.59863 | 214.08865 | 49.9046 |
| 2 | 12.164 | BB | 0.4204 | 4661.35596 | 167.66290 | 50.0954 |

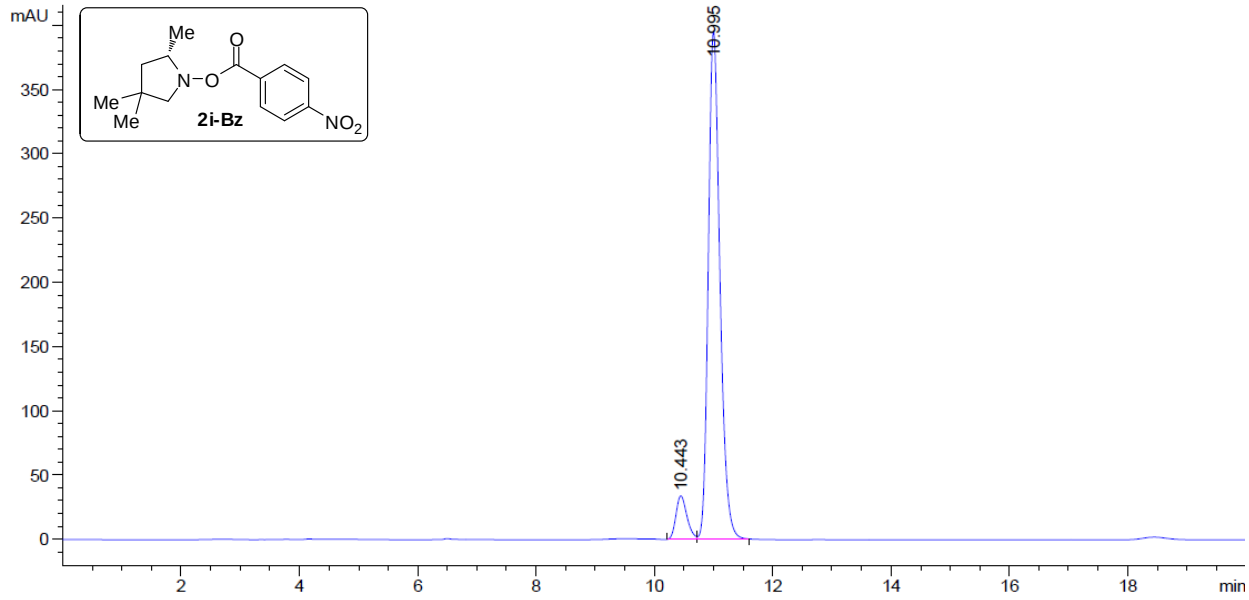



**(*S*)-2,4,4-trimethylpyrrolidin-1-yl 4-nitrobenzoate (2i-Bz):** According to the general procedure (method B) with the exception that **3e** was used as the catalysy, hydroxylamine **1i** (0.24 mmol) was reacted for 2 h at 3 ºC to give the desired *O*-benzoylated hydroxylamine **2i-Bz** (60.9 mg, 91% yield) as a clear oil. $[\alpha]_D^{25}$=38.2º (c=0.82, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.27 (d, *J* = 8.7 Hz, 2 H), 8.16 (d, *J* = 8.7 Hz, 2 H), 3.58 - 3.38 (m, 2 H), 2.83 (d, *J* = 10.1 Hz, 1 H), 1.84 (dd, *J* = 7.3, 12.8 Hz, 1 H), 1.49 (m, 1 H), 1.24 (d, *J* = 6.0 Hz, 3 H), 1.21 (s, 3 H), 1.16 (s, 3 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 163.4, 150.4, 134.8, 130.4, 123.5, 70.1, 63.7, 45.1, 35.3, 30.6, 30.1, 17.8; FTIR (neat, $cm^{-1}$): 3112 (w), 2960 (m), 2868 (m), 1742 (s), 1607 (m), 1526 (s), 1347 (s), 1258 (s); LRMS $[M+H]^+$ calculated for $C_{14}H_{18}N_2O_4$: 279.13, found: 279.1



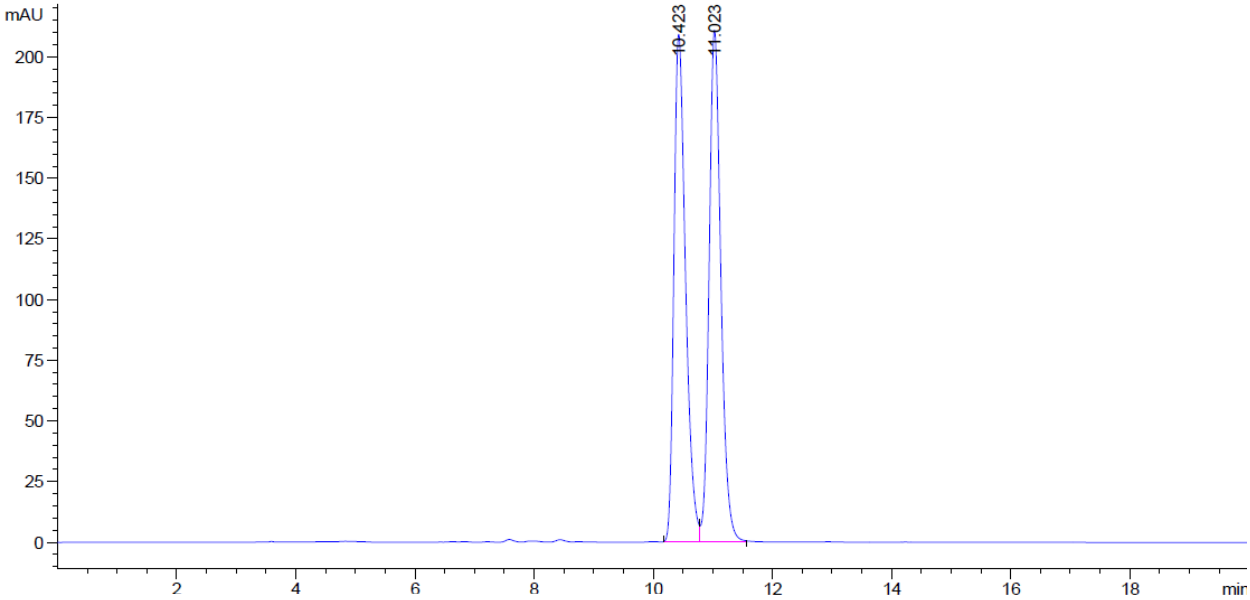



**Enantioenriched Sample:** HPLC (ChiralPak AD-H, 5% IPA/hexanes, 1 mL/min, 254 nm), 85% ee




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 10.443 | BV | 0.1991 | 439.50363 | 33.93535 | 7.5394 |
| 2 | 10.995 | VB | 0.2090 | 5389.92773 | 395.59189 | 92.4606 |

**Racemic Sample:** HPLC (ChiralPak AD-H, 5% IPA/hexanes, 1 mL/min, 254 nm)



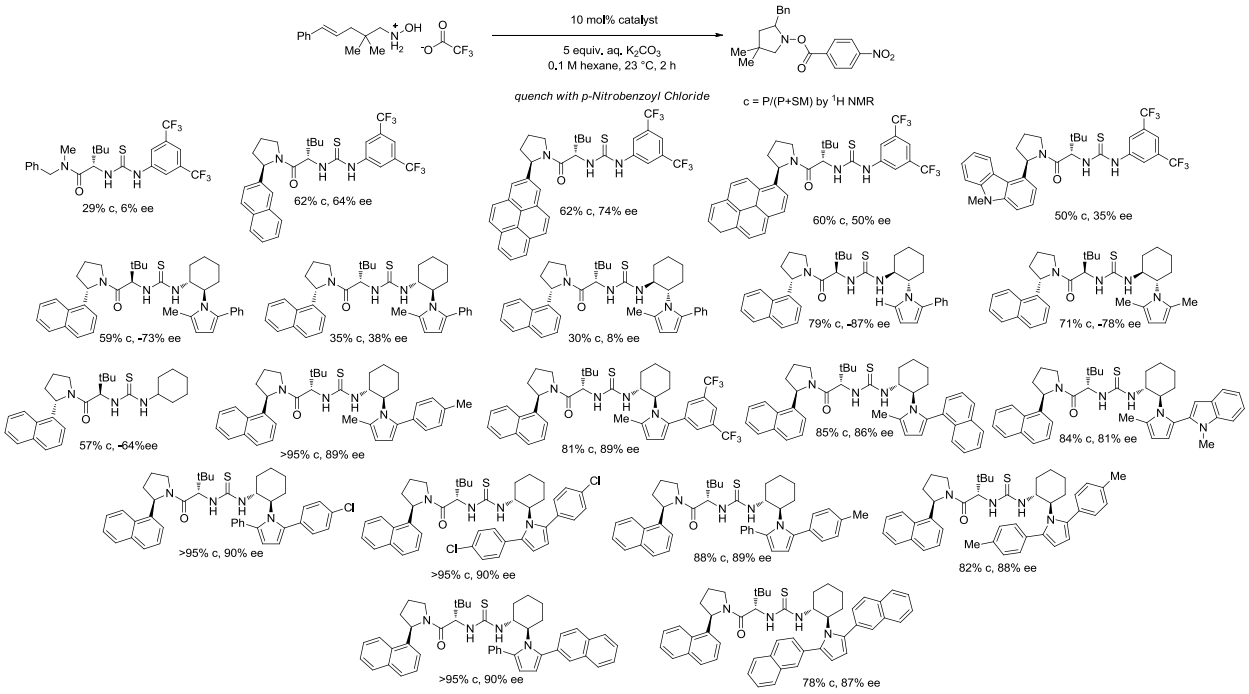

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 10.423 | BV | 0.2082 | 2836.30811 | 209.16263 | 49.5953 |
| 2 | 11.023 | VB | 0.2075 | 2882.59668 | 210.84422 | 50.4047 |

## 6. Additional Catalyst Optimization Data

Catalytic hydroamination procedure for data presented below:

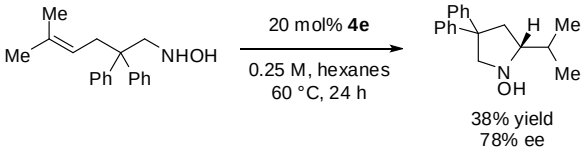
**Deprotection:** To a solution of Boc-protected hydroxylamine **S5a** (101 mg, 0.25 mmol) in dichloromethane (2.4 mL) was added trifluoroacetic acid (0.6 mL). The mixture was stirred for 1 h at 23 ºC, then concentrated *in vacuo* to yield salt **S6a**. The salt was left under reduced pressure (~0.5 torr) for 1 h, and then dissolved in dichloromethane (2.25 mL). 0.5 mL of solution was added to each of four one-dram vials, and the contents of the vials were concentrated. To one vial, mesitylene was added as an internal standard, and the amount of salt in that vial was determined by $^1$H NMR (0.046-0.049 mmol), which provided the amount of salt in the remaining three vials for the catalyst screening reactions.

**Hydroamination:** To a one dram vial containing trifluoroacetate salt **S6a** (0.046 mmol) was added hexanes (0.46 mL) and catalyst (0.0046 mmol). 20% aq. potassium carbonate (0.153 mL, 0.23 mmol) was added, and the mixture was stirred ***vigorously*** for 2 h. A portion of the organic phase was removed by pipette, and to this aliquot was addied *p*-Nitrobenzoyl chloride (34 mg, 0.18 mmol), dichloromethane (2 mL) and triethylamine (0.05 mL, 0.36 mmol). The mixture was stirred for 2 h. 20% aq. potassium carbonate (5 mL) was added, and the organics were extracted with dichloromethane (3 x 5 mL), dried over sodium sulfate, and concentrated *in vacuo*. The ratio of benzoylated product to starting material was determined by $^1$H NMR. The *O*-benzoylated product was purified by flash chromatography on silica gel and the enantiomeric excess was determined by HPLC analysis.

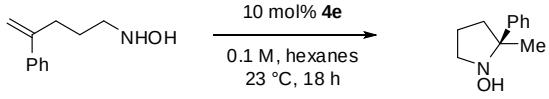


## 7. Additional Substrate Scope and Limitations Data

Results for substrates with varied olefin substitution are presented below, as are results for substrates yielding six-membered ring products. The enantioselective cyclization of the trisubstituted olefin is particularly notable, as asymmetric hydroaminations of this class of olefin are quite rare.[7]



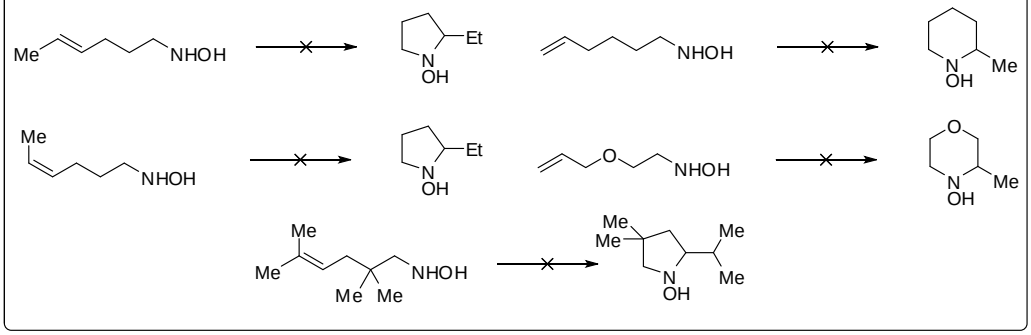

38% yield
78% ee




65% conv.
31% ee

Reactions were performed on a 0.05 mmol scale, and were quenched by the addition of p-$NO_2$ benzoyl chloride. Yields and conversions were determined by $^1$H NMR analysis using mesitylene as an internal standard. Enantioselectivity determined by HPLC analysis.

*No cyclization observed even at elevated temperatures*

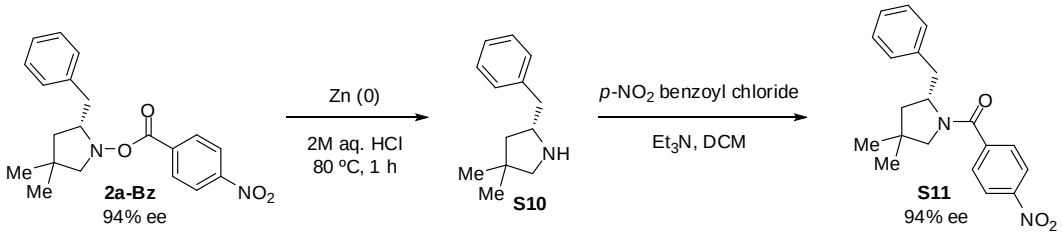



[7]Chapurina, Y.; Ibrahim, H.; Guillot, R.; Kolodziej, E.; Collin, J.; Trifonov, A.; Schulz, E.; Hannedouche, J. *J. Org. Chem.* **2011**, *76*, 10163

## 8. Reduction of *O*-Benzoylated Products

Hydroxylamines can be reduced to the corresponding amine under a variety of conditions.[8]

**Reduction of *O*-benzoylated hydroxylamine product 2a-Bz:**




To **2a-Bz** (24 mg, 0.068 mmol) was added water (2.5 mL) and zinc powder (44.5 mg, 0.68 mmol). The mixture was stirred, and concentrated HCl (0.5 mL) was added slowly. A reflux condenser was fitted to the flask, and the mixture was heated at 80 ºC for 1 h. The mixture was cooled to 0 ºC, and 4M sodium hydroxide was added (3 mL). The aqueous phase was extracted with dichloromethane (3 x 15 mL). The organics were dried over sodium sulfate, and concentrated *in vacuo* to give amine **S10** (75% yield by $^1$H NMR analysis using mesitylene as internal standard). The spectral data for **S10** matched those reported in the literature.[9]

**S10** was benzoylated in order to facilitate analysis by HPLC.

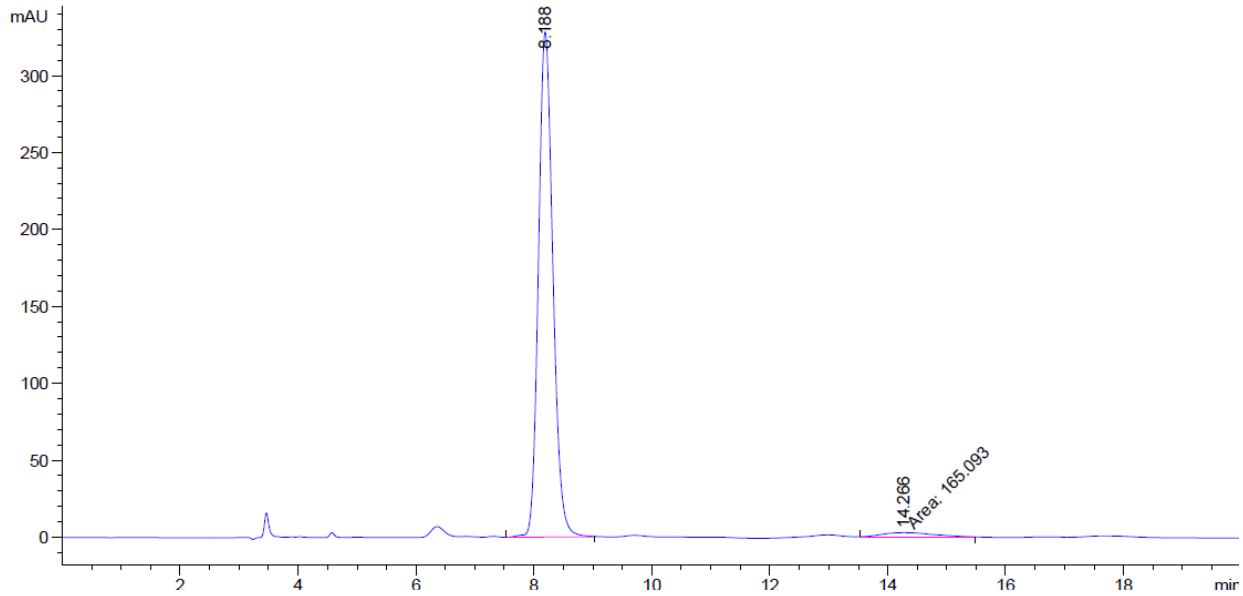
To a solution of amine **S10** (0.051 mmol) in dichloromethane (2 mL) was added *p*-$NO_2$ benzoyl chloride (28 mg, 0.15 mmol) and triethylamine (0.042 mL, 0.3 mmol). The reaction was stirred for 14 h, then quenched by the addition of 20% aq. potassium carbonate (2 mL). The organics were extracted with dichloromethane, concentrated *in vacuo* and purified by chromatography on silica gel to give the product as a white solid.

**(2-benzyl-4,4-dimethylpyrrolidin-1-yl)(4-nitrophenyl)methanone (S11):** $[\alpha]_D^{23}$=132.6 º (c=0.46, $CHCl_3$); $^1$H NMR (500MHz ,$CDCl_3$) δ = 8.29 (d, *J* = 8.7 Hz, 2 H), 7.68 (d, *J* = 8.7 Hz, 2 H), 7.38 - 7.32 (m, 2 H), 7.30 - 7.25 (m, 3 H), 4.65 - 4.52 (m, 1 H), 3.30 (dd, *J* = 3.2, 12.8 Hz, 1 H), 3.00 (dd, *J* = 8.5, 13.0 Hz, 1 H), 2.95 (s, 2 H), 1.79 (dd, *J* = 7.6, 12.6 Hz, 1 H), 1.65 (dd, *J* = 10.1, 12.4 Hz, 1 H), 0.98 (s, 3 H), 0.89 (s, 3 H); $^{13}$C NMR (126MHz ,$CDCl_3$) δ = 167.9, 148.6, 142.9, 137.8, 129.8, 128.5, 128.3, 126.5, 123.7, 63.0, 58.1, 43.8, 38.7, 38.2, 25.5, 25.5; FTIR: 3106 (w), 3028 (w), 2958 (m), 2869 (m), 1631 (s), 1522 (s), 1494 (m), 1422 (s), 1349 (s), 1292 (m), 1210 (m); LRMS $[M+H]^+$ calculated for $C_{20}H_{23}N_2O_3$: 339.16, found: 339.2

For enantioenriched **2a-Bz** (94% ee) no erosion of enantioenrichment was observed during the sequence – see HPLC analysis of **S11** below.

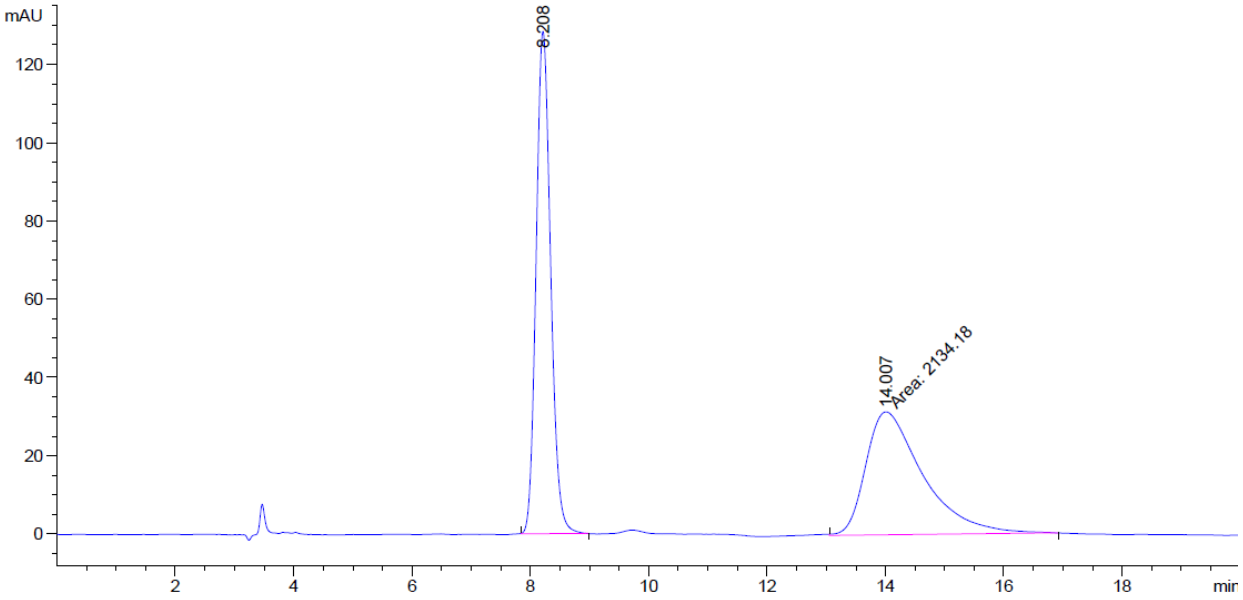
[8] See Cicci, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773 and references therein.
[9] Zhang, X.; Emge, T. J.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 394.

**Enantioenriched Sample:** HPLC (ChiralPak OD-H, 20% IPA/hexanes, 1 mL/min, 210 nm), 94% ee




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.188 | VB | 0.2635 | 5618.39404 | 328.55508 | 97.1454 |
| 2 | 14.266 | MM | 0.9837 | 165.09334 | 2.79711 | 2.8546 |

**Racemic Sample:** HPLC (ChiralPak OD-H, 20% IPA/hexanes, 1 mL/min, 210 nm)




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.208 | BB | 0.2654 | 2197.92627 | 128.57405 | 50.7357 |
| 2 | 14.007 | MM | 1.1277 | 2134.18457 | 31.54045 | 49.2643 |

## 9. Absolute Stereochemistry Determination

Absolute stereochemistry was determined by derivatization of the pyrrolidine **S10** to corresponding Mosher amide and comparison of the $^{19}F$ spectroscopic data to the previously assigned configuration for that compound.[9,10]

### Procedure for Mosher amide formation and $^{19}F$ NMR Analysis:

(*R*)-Mosher acid was converted to the corresponding (*S*)-Mosher acid chloride according to the literature procedure.[11]

Amine **S10** (0.04 mmol) was diluted with $CDCl_3$ (1.0 mL). DIPEA (0.017 mL, 0.1 mmol) and (*S*)-Mosher acid chloride (0.6 mmol) were added to the mixture with stirring. After 5 minutes, the reaction mixture was analyzed by $^{19}F$ NMR analysis at 50 ºC.

**Mosher adduct:** $^{19}F$ NMR ($CDCl_3$, 50 ºC) $\delta$ −70.0 (major), −71.0 (minor). Referenced to the (*S*)-Mosher acid chloride resonance at −70.5

## 10. Calculations

Calculations were executed at Harvard University on the Odyssey research computing cluster using the Gaussian 03[12] program with the B3LYP[13] method. The 6-311+G(d,p) basis sets of Pople and co-workers was used.[14] All stationary points are fully optimized and verified by frequency calculations using the rigid-rotor/harmonic-oscillator assumption. Transition structures were characterized by the existence of a single imaginary frequency corresponding to the process of interest and local minima were characterized by the absence of any imaginary frequencies. Energies are reported in units of hartrees.

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[10] Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

[11] Smith, P. M.; Thomas, E. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3541.

[12] Gaussian 03, Revision E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

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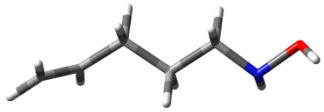
[14] (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys*. **1972,** *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta.* **1973**, *28*, 213.



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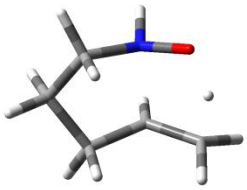
| H | 4.58147700 | -0.57175000 | -0.43938300 |
| H | 3.64671700 | 0.83789800 | -1.18398000 |
| C | 2.63668600 | -0.25093600 | 0.31995900 |
| H | 2.71023100 | -1.08632000 | 1.01574300 |
| N | -2.30526600 | -0.50531100 | -0.26580900 |
| H | -2.32633700 | -1.27524700 | 0.40091000 |
| O | -3.54145400 | 0.19552000 | 0.00268800 |
| H | -3.99961500 | 0.16140100 | -0.84372700 |
| C | 1.33837000 | 0.50536100 | 0.34147200 |
| H | 1.38954200 | 1.34375700 | -0.36144300 |
| H | 1.19329500 | 0.93952500 | 1.33974700 |
| C | -1.19582400 | 0.38248700 | 0.09291200 |
| C | 0.12570700 | -0.38160900 | 0.00683400 |
| H | -1.33101700 | 0.80597300 | 1.09897800 |
| H | -1.19845400 | 1.21540800 | -0.61621400 |
| H | 0.10226400 | -1.23380300 | 0.69870100 |
| H | 0.24073900 | -0.79786100 | -0.99846100 |



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**Imaginary Frequencies: 1**

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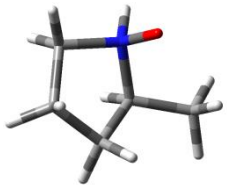
|---|---|---|---|
| C | -1.81752300 | -0.92195600 | -0.18579800 |
| H | -2.71266500 | -1.09716600 | 0.40583900 |
| H | -1.87222100 | -1.31147000 | -1.20087100 |
| C | -0.57181500 | -0.99594100 | 0.47013900 |
| H | -0.56068300 | -1.09278200 | 1.55332300 |
| N | -0.11723800 | 1.03974200 | 0.43259800 |
| H | -0.08783200 | 1.41659800 | 1.37748600 |
| O | -1.16340100 | 1.52144200 | -0.25368900 |
| H | -1.77227700 | 0.42705300 | -0.37844000 |
| C | 0.70840900 | -1.40149300 | -0.22195600 |
| H | 0.52690600 | -1.49012700 | -1.29841300 |
| H | 1.02886300 | -2.38819200 | 0.13018000 |
| C | 1.80981300 | -0.35751200 | 0.03345300 |

| | | | |
|---|---|---|---|
| C | 1.19265000 | 1.01576200 | -0.24010200 |
| H | 1.82544500 | 1.84153100 | 0.09890100 |
| H | 0.98869000 | 1.15519900 | -1.30297400 |
| H | 2.14527000 | -0.41542000 | 1.07574800 |
| H | 2.68917600 | -0.52811900 | -0.59387100 |



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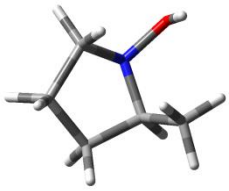
**Imaginary Frequencies: 0**

| | | | |
|---|---|---|---|
| C | 2.17243500 | 0.27683000 | 0.05529800 |
| H | 2.20813000 | -0.15488400 | -0.94532900 |
| H | 2.73245200 | -0.37185800 | 0.73522600 |
| C | 0.72577200 | 0.41824400 | 0.48228800 |
| H | 0.65763300 | 0.67641000 | 1.54683600 |
| N | -0.03136100 | -0.90835400 | 0.33730900 |
| H | 0.24982000 | -1.53010400 | 1.11182700 |
| O | 0.16472000 | -1.50714900 | -0.86168500 |
| H | 2.65445900 | 1.25800000 | 0.05154700 |
| C | -0.14209800 | 1.37577600 | -0.34734500 |
| H | 0.21412600 | 1.39453200 | -1.37761900 |
| H | -0.07699300 | 2.39025400 | 0.05080900 |
| C | -1.58572600 | 0.80326400 | -0.28261200 |
| C | -1.46666500 | -0.49011200 | 0.53539000 |
| H | -1.63031100 | -0.31841400 | 1.60516200 |
| H | -2.09008400 | -1.31092300 | 0.18978900 |
| H | -2.28626600 | 1.49433700 | 0.18981400 |
| H | -1.95351200 | 0.58431000 | -1.28385600 |



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**Imaginary Frequencies: 0**

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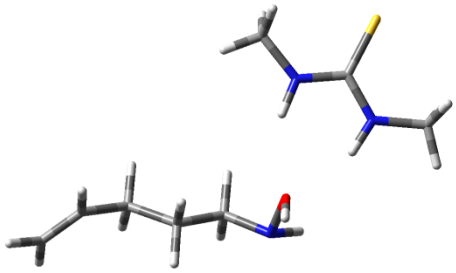
| H | -0.29240700 | 1.30710400 | 1.62967600 |
| H | -1.74531900 | 1.68990300 | 0.68123700 |
| C | -0.12946600 | 0.82039700 | -0.51319400 |

| | | | |
|---|---|---|---|
| H | -0.49110300 | 1.25771400 | -1.44706100 |
| N | -0.53346200 | -0.60397200 | -0.50079100 |
| O | -1.91562300 | -0.80939900 | -0.27404700 |
| H | -0.31009100 | 2.69661200 | 0.54507900 |
| C | 1.40284600 | 0.66856600 | -0.51316700 |
| H | 1.89261300 | 1.53853600 | -0.07165400 |
| H | 1.76525300 | 0.57149500 | -1.53772500 |
| C | 1.68448800 | -0.64232800 | 0.28268900 |
| C | 0.29943900 | -1.28202600 | 0.49440500 |
| H | 0.27635800 | -2.35921600 | 0.32335300 |
| H | -0.06989200 | -1.09897600 | 1.51980800 |
| H | 2.34016200 | -1.30387700 | -0.28482100 |
| H | 2.17279100 | -0.44390300 | 1.23836200 |
| H | -2.10987200 | -0.52908900 | 0.63770300 |



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**Multiplicity: 1**
**E = –954.09497369**
**Imaginary Frequencies: 0**

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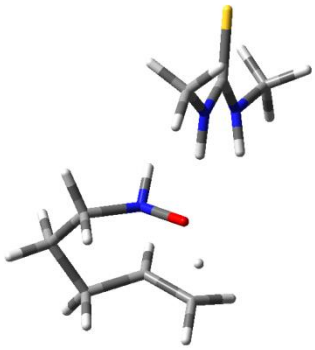
| N | -1.10540200 | 2.13222700 | 0.11811100 |
| O | -0.22156800 | 1.49381200 | -0.84388500 |
| H | 1.72691000 | -2.85370200 | 0.71167400 |
| C | 1.47981500 | -2.44748200 | -0.27186700 |
| H | 0.43601500 | -2.67034900 | -0.50107500 |
| H | 2.12184700 | -2.93906700 | -1.00732900 |
| N | 1.64650400 | -1.00504900 | -0.30167000 |
| C | 2.82689700 | -0.37402100 | -0.05409800 |
| H | 0.85035000 | -0.43743600 | -0.55996400 |
| N | 2.77084600 | 0.98167200 | -0.15985700 |
| C | 3.91787500 | 1.85445100 | 0.01918100 |
| H | 1.89271500 | 1.39633400 | -0.44398200 |
| H | 3.58201200 | 2.88409700 | -0.11846300 |
| H | 4.34394400 | 1.74615700 | 1.01910400 |
| H | 4.70605100 | 1.63378100 | -0.70557800 |
| S | 4.23644200 | -1.20102800 | 0.35410400 |
| C | -1.91167400 | 1.09812200 | 0.77635100 |
| H | -2.32649300 | 1.58564700 | 1.66650100 |
| H | -1.28725200 | 0.26117800 | 1.12121500 |
| H | -0.48058000 | 1.88914900 | -1.68387900 |
| H | -0.45573200 | 2.51880600 | 0.79900000 |
| C | -3.04180000 | 0.59272100 | -0.11731200 |
| H | -3.64976500 | 1.44407400 | -0.43923900 |
| H | -2.61390100 | 0.14661000 | -1.02168100 |
| C | -3.93158100 | -0.44427000 | 0.59058200 |

| | | | |
|---|---|---|---|
| H | -4.38506900 | 0.00065500 | 1.48325300 |
| H | -3.30096700 | -1.27355100 | 0.93898000 |
| C | -5.01014700 | -0.99111200 | -0.30185700 |
| H | -4.66770400 | -1.50011000 | -1.20225400 |
| C | -6.31812900 | -0.89255800 | -0.07619600 |
| H | -6.70744700 | -0.39480800 | 0.80721700 |
| H | -7.04664500 | -1.30857500 | -0.76288000 |



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**Multiplicity: 1**
**E = –954.06448261**
**Imaginary Frequencies: 1**

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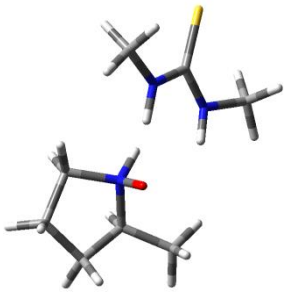
| H | 2.79677300 | 2.35371200 | 1.62413300 |
| H | 3.72048300 | 0.84558400 | 2.09219500 |
| C | 3.19060600 | 0.98334200 | 0.02544800 |
| H | 2.90816700 | 1.71113400 | -0.73066900 |
| N | 1.40717700 | -0.16752000 | -0.16552600 |
| H | 0.70763300 | 0.24720500 | -0.78043700 |
| O | 0.98376700 | -0.12321800 | 1.12078900 |
| H | 1.88645100 | 0.61196300 | 1.55593900 |
| H | -2.72282700 | -2.71236100 | -0.04319300 |
| C | -2.57804700 | -2.22393200 | 0.92467200 |
| H | -1.97583000 | -2.86733500 | 1.56828800 |
| H | -3.56225200 | -2.08375200 | 1.37686400 |
| N | -1.88401200 | -0.95606300 | 0.78581000 |
| C | -2.36350500 | 0.09183600 | 0.07099900 |
| H | -0.94508000 | -0.87669500 | 1.16484300 |
| N | -1.51873200 | 1.17490900 | 0.03885500 |
| C | -1.93914500 | 2.48011500 | -0.45092800 |
| H | -0.77374500 | 1.16488600 | 0.72742500 |
| H | -1.08380200 | 3.15591300 | -0.38702600 |
| H | -2.26297200 | 2.40865300 | -1.48923300 |
| H | -2.76953300 | 2.89219900 | 0.13176000 |
| S | -3.84493900 | 0.06396400 | -0.72686200 |
| C | 1.96672000 | -1.43874000 | -0.65018300 |
| H | 1.25323400 | -1.96173400 | -1.29344800 |
| H | 2.15000300 | -2.05512900 | 0.23181800 |
| C | 4.06469600 | -0.14715700 | -0.45866700 |
| H | 4.92796100 | 0.26179200 | -0.99511300 |
| H | 4.45517100 | -0.69846800 | 0.40317000 |
| C | 3.27429300 | -1.10120400 | -1.37105800 |

| | | | |
|---|---|---|---|
| H | 3.05464700 | -0.60988300 | -2.32577000 |
| H | 3.84304000 | -2.00614900 | -1.60133800 |



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**E = –954.10632561**
**Imaginary Frequencies: 0**

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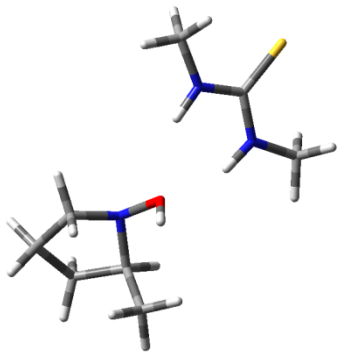
| H | 1.82467400 | 2.73393000 | 0.10755200 |
| H | 3.56263900 | 2.60503400 | 0.39353400 |
| C | 2.69284400 | 0.79993600 | -0.36483100 |
| H | 2.75890300 | 1.04453200 | -1.43171800 |
| N | 1.43162400 | -0.05195500 | -0.23724900 |
| H | 0.65443600 | 0.39208600 | -0.75645600 |
| O | 1.04914800 | -0.23432800 | 1.06955700 |
| H | -2.56812800 | -2.73618600 | -0.37422500 |
| C | -2.35428300 | -2.37495400 | 0.63594700 |
| H | -1.71329000 | -3.09384600 | 1.14947300 |
| H | -3.30604600 | -2.30032200 | 1.16768400 |
| N | -1.66556700 | -1.09839000 | 0.61342400 |
| C | -2.19365300 | 0.03169500 | 0.08996400 |
| H | -0.71040500 | -1.03458200 | 0.97938500 |
| N | -1.35087600 | 1.12167200 | 0.18141700 |
| C | -1.82967800 | 2.47937800 | -0.04330100 |
| H | -0.60313000 | 1.00899900 | 0.86749300 |
| H | -0.98699300 | 3.16149200 | 0.08935300 |
| H | -2.21873700 | 2.58225100 | -1.05610500 |
| H | -2.62910500 | 2.75721900 | 0.65171200 |
| S | -3.71228000 | 0.10376900 | -0.63343200 |
| C | 1.83125000 | -1.34406700 | -0.89720000 |
| H | 1.80229400 | -1.18686900 | -1.97969900 |
| H | 1.10039700 | -2.09914400 | -0.62031600 |
| C | 3.79833100 | -0.19631800 | 0.01311800 |
| H | 4.72840900 | 0.05478200 | -0.49972300 |
| H | 3.98284900 | -0.14966400 | 1.08670300 |
| C | 3.25719300 | -1.59685500 | -0.38528900 |
| H | 3.86228400 | -2.07242800 | -1.15875400 |
| H | 3.23917200 | -2.25947000 | 0.47881300 |
| H | 2.41972200 | 1.81491500 | 1.50647300 |



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**Multiplicity: 1**
**E = –954.10969404**
**Imaginary Frequencies: 0**

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| H | -4.01879500 | -2.31490000 | 0.91178400 |
| C | -2.82669500 | -0.91313000 | -0.21754500 |
| H | -2.27785400 | -1.70953200 | -0.72598400 |
| N | -1.91999000 | 0.25404100 | -0.10377100 |
| O | -0.89904500 | 0.09145300 | 0.87448600 |
| H | 3.03787500 | 2.68475500 | -0.71409600 |
| C | 2.62451800 | 2.44451000 | 0.26910800 |
| H | 1.86960700 | 3.18796200 | 0.53235900 |
| H | 3.44043200 | 2.48943100 | 0.99440400 |
| N | 1.98777500 | 1.14024400 | 0.27371100 |
| C | 2.63791600 | -0.02122600 | -0.00405900 |
| H | 0.99297900 | 1.09336200 | 0.45189600 |
| N | 1.84811700 | -1.12754600 | 0.03075100 |
| C | 2.32366900 | -2.47013200 | -0.24823700 |
| H | 0.86648600 | -1.00002800 | 0.23919000 |
| H | 1.47876700 | -3.15400600 | -0.14585200 |
| H | 2.72828400 | -2.54830800 | -1.26073700 |
| H | 3.11101400 | -2.76587200 | 0.44947600 |
| S | 4.28612300 | -0.08531300 | -0.35653000 |
| C | -2.75403400 | 1.43091200 | 0.16449300 |
| H | -2.19646600 | 2.33968100 | -0.06583500 |
| H | -3.05070500 | 1.47801100 | 1.22655400 |
| C | -3.91808800 | -0.31215900 | -1.12157900 |
| H | -3.63646400 | -0.42855400 | -2.16896500 |
| H | -4.87600600 | -0.81497600 | -0.97931900 |
| C | -3.97558200 | 1.19981700 | -0.74530400 |
| H | -3.92272200 | 1.82165200 | -1.63931000 |
| H | -4.89974200 | 1.45709700 | -0.22565300 |
| H | -3.97489600 | -0.71572200 | 1.65044300 |
| H | -1.31431600 | 0.04817000 | 1.75417300 |