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# Amino Imidate-Catalyzed Asymmetric Michael Reactions of Ketones and Nitroalkenes

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* indicates the main/corresponding author. Use another symbol to indicate equal contributions.

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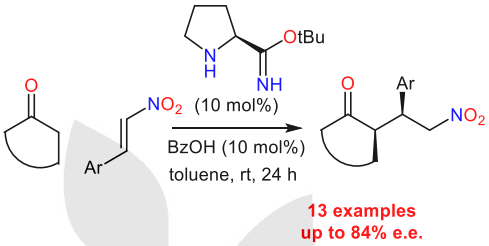


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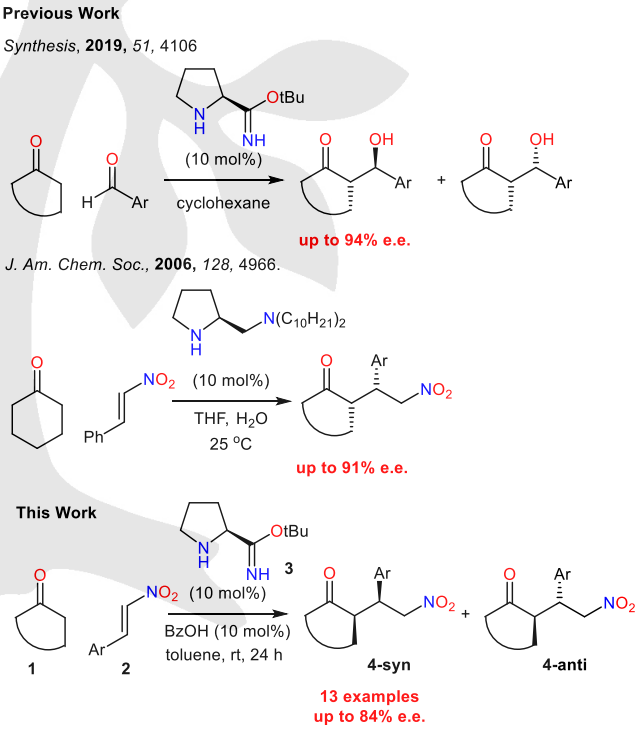
**Abstract** The efficiency of an amino imidate organocatalyst was evaluated in the Michael reaction of ketones with nitroalkenes. *tert*-Butyl L-proline imidate was found to be a *syn*-selective catalyst generating products with moderate to good enantioselectivities, of up to 84% e.e. The best substrates were found to be cyclic ketones and β-nitrostyrenes. The catalytic efficiency and enantioselectivity was enhanced by the addition of 10 mol% of benzoic acid.

**Key words** asymmetric synthesis, organocatalysis, Michael reaction, amino imidate

Since the initial discovery of organocatalysis[1] which was generalized by List, Barbas[2] and MacMillan,[3] which led to the award of the 2021 Nobel Prize in Chemistry, there has been considerable interest in the study of small organic molecules capable of catalyzing a wide range of synthetic transformations enantioselectively. The pyrrolidine ring is a privileged structure regarding catalytic ability, and it is often substituted with carboxylic acids,[2] amides,[4] esters,[5] tetrazoles[6] or silyl ethers of tertiary alcohols.[7] Each of these modifications bestow subtle changes to catalytic ability, enantioselectivity, diastereoselectivity and the types of reaction which can be catalyzed. The most important of these reactions are aldol condensations,[8] Diels-Alder cycloadditions[9] and Michael additions,[8a,b, 10] all of which lead to valuable chiral products from simple achiral starting materials. Michael reactions, especially onto nitroalkenes have been of interest to several research groups.[11] Proline itself was shown to be a relatively poor catalyst generating products with enantioselectivities <25%.[12] Highly functionalized and sterically bulky proline derivatives give products in much greater enantioselectivities 60-95% but can involve protracted synthesis.[13] We recently reported the serendipitous discovery of a new type of pyrrolidine-containing organocatalyst, the *tert*-butyl imidate of proline **3**, and its ability to catalyze asymmetric aldol reactions in good to high enantiomeric excesses[14] (Scheme 1). In this paper we further explore the scope of proline *tert*-butyl imidate **3** as an enantioselective organocatalyst for the Michael addition of cyclic ketones, heteroatom-containing cyclic ketones, and aldehydes to several nitroalkenes (Scheme 1).



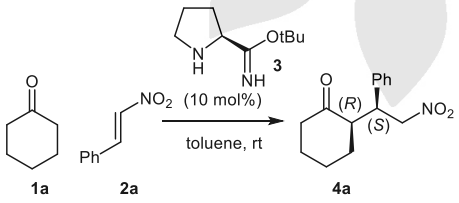

**Scheme 1.** *tert*-Butyl Proline Imidate and Proline Amine Catalyzed Reactions.

Initial studies focused on the Michael reaction of cyclohexanone with β-nitrostyrene, as the reaction is well benchmarked in the literature and the products are well characterized.[11c] In our earlier work on the amino imidate catalyzed aldol reaction it was noted that the reaction solvent played a significant role in both the conversion to products and the enantioselectivity of the

reaction. Therefore, a screen of reaction solvents was undertaken with this standard reaction.

Cyclohexanone **1a** and β-nitrostyrene **2a** were stirred in the presence of 10 mol% of proline *tert*-butyl imidate **3** at room temperature in a variety of solvents (Table 1). As can be seen the reaction proceeded poorly when highly dipolar aprotic solvents (entries 1 and 2) and polar protic solvents (entries 11-13) were used. The other solvents, both dipolar and non-polar, all gave reasonable to excellent conversions, generally above 90% (entries 4-10). The reaction was the most diastereoselective when non-polar solvents such as cyclohexane, $CH_2Cl$ or toluene [2] were used (entries 6, 8 and 10), giving *syn*/*anti* ratios of greater than 9:1. Determination of the enantioselectivity of the reactions showed that non-polar hydrocarbon solvents were preferable, generating products with the highest enantioselectivities of 39% and 43% for cyclohexane and toluene respectively (entries 6 and 10). The absolute stereochemistry (1*R*, 2*S*) of the major (*syn*) diastereomer was confirmed by comparison of the optical rotation and HPLC retention times with literature data.[11c, 15] The other solvents led to products with much lower enantioselectivities. These trends can be rationalized by the general preference for non-polar solvents in the synthesis of enamines from ketones and amines, and the ability of highly dipolar or polar protic solvents to form competing hydrogen bonds with the amino imidate catalyst, which can disrupt the formation of hydrogen bonds between the catalyst and the substrate essential for enhanced enantioselectivity. While the catalyst was not recovered from these reactions, it was clearly visible in the $^1$H NMR of the crude reaction mixture and there was no evidence of its hydrolysis to proline amide. These results, combined with solubility considerations of the substrates led to the selection of toluene as the solvent of choice.

**Table 1.** Initial Solvent Screen.



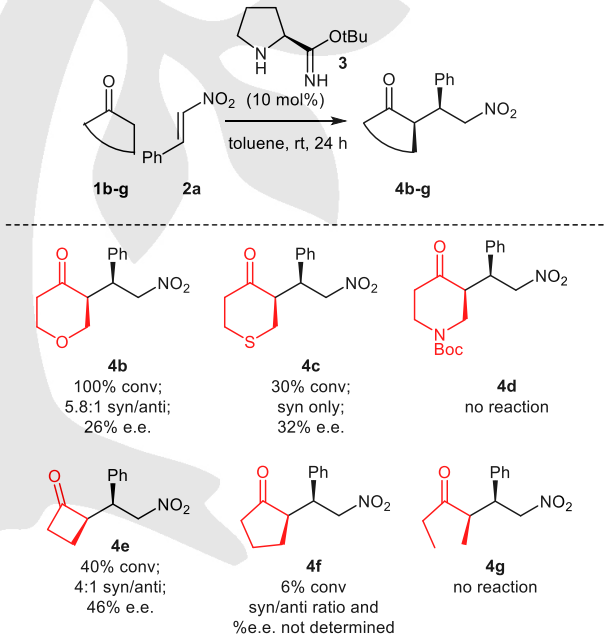

| Entry | Solvent | Conversion (%)[a] | *syn*:*anti* ratio[b] | %ee (*syn*) [c] |
|---|---|---|---|---|
| 1 | DMF | 14 | 1:trace | [d] |
| 2 | DMSO | 0 | - | - |
| 3 | Dioxane | 63 | 7:1 | 29 |
| 4 | MeCN | 92 | 8:1 | 7 |
| 5 | THF | 99 | 8:1 | 19 |
| 6 | Cyclohexane | 100 | 10.7:1 | 39 |
| 7 | EtOAc | 100 | 9:1 | 22 |
| 8 | $CH_2Cl_2$ | 100 | 12.6:1 | 21 |
| 9 | Diethyl carbonate | 88 | 5.6:1 | 28 |
| 10 | Toluene | 100[d] | 9.7:1 | 43 |
| 11 | MeOH | 11 | 6.6:1 | [e] |
| 12 | MeOH/IPA 1:1 | 6 | 6:1 | [e] |
| 13 | EtOH/IPA 1:1 | 14 | 5.8:1 | [e] |

[a] Determined by 400 MHz $^1$H NMR after 24 hours. [b] Determined by 400 MHz $^1$H NMR. [c] Determined by HPLC chiralpak AS-H column (see supporting information). [d] Conversion was only 49% after 8 hours, as determined by 400 MHz $^1$H NMR. [e] Not determined.

In an attempt to increase the enantioselectivity of the reaction two changes were made, (i) the temperature was reduced to 0 °C and, (ii) 20 mol% of catalyst was used. In the reaction where the temperature was lowered to 0 °C, the conversion dropped to 60% and the enantioselectivity of the **4a** dropped to 27%, while the *syn*/*anti* ratio increased to 10.3:1. Increasing the catalyst loading to 20 mol% had no effect on either the diastereo- or enantioselectivity of the reaction.

With these results in hand the scope of the ketone partner was examined (Table 2). Tetrahydropyran-4-one **1b** underwent a smooth and complete reaction in 24 hours and generated the *syn*-diastereomer as the major product (5.8:1 dr) in 26% e.e. All other ketones showed low levels of conversion and only modest levels of enantioselectivity, with *N*-Boc-piperidine-4-one **1d** and pentan-2-one **1g** not reacting at all. While these reactions did not work well, they did provide the impetus to investigate ways to improve both the conversion and levels of enantioinduction.

**Table 2.** Ketone Scope[a]

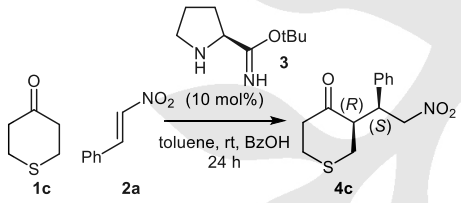



[a] conversion and *syn*/*anti* ratios determined by 400 MHz $^1$H NMR after 24 hours. %e.e. determined by chiral stationary phase HPLC (see supporting information).

Benzoic acid has been reported as beneficial additives in the Michael reaction of ketones and nitroalkenes,[16] so it was decided to investigate its effect on the reaction of tetrahydrothiopyran-4-one **1c** with β-nitrostyrene **2a**. This reaction was chosen to

determine the effect of benzoic acid on the conversion, diastereo- and enantioselectivity (Table 3). As can be seen the introduction of benzoic acid had a dramatic and beneficial effect on the conversion and enantioselectivity of the reaction. The addition of just 10 mol% of benzoic acid (entry 1) led to complete consumption of the nitroalkene and generated the *syn*-adduct in 71% e.e., a vast improvement over the 30% conversion with 32% e.e. from the reaction without benzoic acid. The absolute stereochemistry (1*R*, 2*S*) of the major (*syn*) diastereomer was confirmed by comparison of the optical rotation and HPLC retention times with literature data.[15] The diastereomeric ratio was eroded slightly, with the reaction now producing an 8:1 mixture of *syn*/*anti* diastereomers. Increasing the amount of benzoic acid further resulted in a gradual reduction in the amount of product produced, presumably as a greater proportion of the pyrrolidine nitrogen in the catalyst was protonated and hence no longer able to participate in the reaction (entries 2-4). We propose that benzoic acid serves two roles, which accounts for its beneficial effects on the reaction. The first is that at low concentrations it aids the formation of the enamine nucleophile by protonation of the carbonyl group. The second is that it can activate the nitroalkene by simultaneously hydrogen bonding to the nitro group and the imidate in the transition state of the Michael addition, which could also account for the increase in the enantioselectivity of the reaction (Figure 1).

**Table 3.** The Effect of Benzoic acid on the Reaction of **1c** with **2a**




| Entry | BzOH (mol%) | Conversion (%)[a] | *syn*:*anti* ratio[b] | %ee (*syn*)[c] |
|---|---|---|---|---|
| 1 | 10 | 100 | 8:1 | 71 |
| 2 | 50 | 90 | 7.5:1 | 72 |
| 3 | 100 | 59 | 6:1 | 66 |
| 4 | 150 | 49 | 8.6:1 | 80 |

[a] Determined by 400 MHz $^1$H NMR after 24 hours. [b] Determined by 400 MHz $^1$H NMR. [c] Determined by chiral stationary phase HPLC (see supporting information).

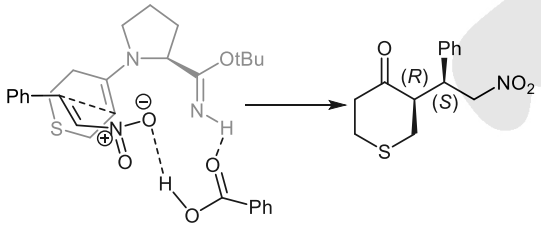
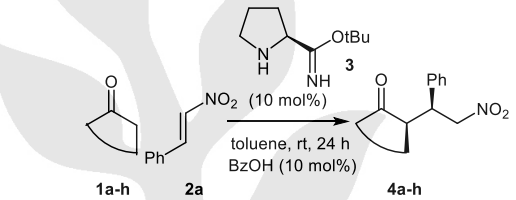
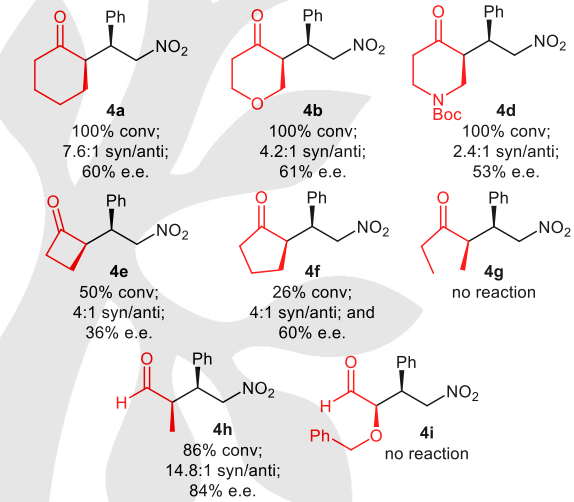



**Figure 1.** Proposed Transition State and the Role of Benzoic Acid.

With the beneficial effect of benzoic acid verified, the reactions with substrates **1a-h** were re-examined (Table 4). In the case of cyclohexanone **1a**, the %ee of **4a** increased from 43% to 60% and for the reaction of ketone **1b** the %ee of **4b** increased from 26% to 61%. Interestingly, in the case of ketone *N*-Boc-piperidine-4-one **1d**, which did not react under the initial conditions, the reaction went to completion and generated **4d** as the major product in 53% e.e. Under the benzoic acid conditions **4f** was now formed with a moderate 26% conversion and in 60% e.e. Only the reactions to generate substrates **4e** and **4g** were unimproved by the addition of benzoic acid. In a further extension of the scope of the reaction propanal **1h** was condensed with **2a** to give **4h** as the major product (14.8:1 *syn*/*anti* ratio) in 84% e.e., with an 86% conversion. Unfortunately, the use of other functionalized aldehydes such as benzyloxy acetaldehyde **1i** did not result in any reaction.

**Table 4.** Ketone and Aldehyde Scope with Benzoic Acid Additive[a]

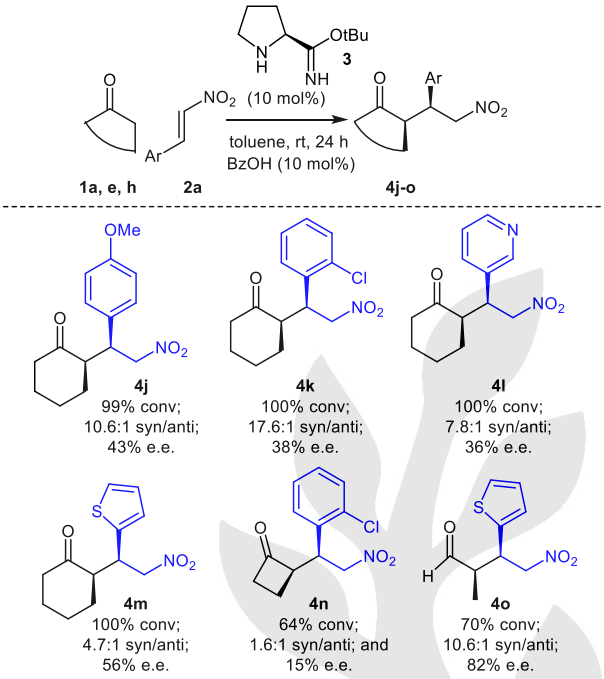



[a] conversion and *syn*/*anti* ratios determined by 400 MHz $^1$H NMR after 24 hours. %e.e. determined by chiral stationary phase HPLC (see supporting information).

With the scope and limitations of the ketone substrate investigated, attention turned to a study on the scope of the nitroalkene partner. To this end **1a**, **1e** and **1h** were reacted with nitroalkenes **2b-d** (Table 5).

**Table 5.** Nitroalkene Scope[a]




[a] conversion and *syn/anti* ratios determined by 400 MHz $^1$H NMR after 24 hours. %e.e. determined by chiral stationary phase HPLC (see supporting information).

All nitroalkenes used in the reaction resulted in the formation of enantioenriched products. Both electron rich **4j** and electron poor **4l** were produced quantitatively and in moderate %e.e. *ortho*-Substituted aryl nitroalkenes also participated well in their conversion to products **4k** and **4n**. Heteroaromatic nitroalkenes, both electron poor and electron rich could be used in the reaction to generate products **4l**, **4m** and **4o**. Pleasingly, **4o** was formed in a good 82% e.e.

An investigation into the use of *tert*-butyl proline imidate **3** as a catalyst in the Michael reactions of ketones and aldehydes with nitroalkenes was undertaken. These studies showed that imidate catalyst **3** on its own generated moderate amounts of Michael addition products in low to moderate enantioselectivities. However, the catalyst was much more efficient when combined with 10 mol% of benzoic acid. Under these conditions, more product was formed and the enantioselectivities increased markedly, in some cases up to 84%. The reaction was tolerant of a range of cyclic ketones, heteroatom-containing cyclic ketones and simple aldehydes, with six-membered cyclic ketones and propanal being optimal. A range of electron rich, electron poor, *ortho*-substituted and heterocyclic nitroalkenes were investigated and it was shown that they could all be used with equal efficiency. Imidates based on proline are a new class of organocatalyst which may have the potential to become efficient and selective catalyst for a range of transformations. Investigations into the effect of modification of the proline imidate on catalytic activity and enantioselectivity are underway and will be reported in due course.

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Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-d, 7.26 ppm for $^1$H NMR; chloroform-d, 77.0 ppm for $^{13}$C NMR. Coupling constants (J) are quoted in Hertz. Infra-red absorbances were recorded on a PerkinElmer UATR Two FT-IR spectrometer using NaCl plates. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Thin layer chromatography was performed on aluminium sheets coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, basic aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Sigma-Aldrich. Dry solvents were acquired from a PureSolv PS-MD7 solvent tower. High Performance Liquid Chromatography (HPLC) was performed using an Agilent 1200 series instrument using the chiral columns indicated and a range of wavelengths from 210-280 nm for detection.

**Synthesis of Proline Imidate 3**

Boc-*L*-proline (5.01 g, 23.3 mmol) and THF (70 mL) were added to a flask. To this flask, $NEt_3$ (3.25 mL, 23.3 mmol) was added and stirred, at room temperature. After 15 minutes, ethyl chloroformate (2.22 mL, 23.3 mmol) was added and the reaction was continued to be stirred at room temperature. After 1h, 7N solution of $NH_3$ in MeOH (5 mL), was added and the reaction was continued to be stirred overnight. After that, the reaction was deemed complete by $^1$H NMR and the stirring stopped. The solvent was removed in *vacuo* and the solution was washed with $H_2O$ (10 mL) and extracted with DCM (x3). The combined organic layers dried were over $MgSO_4$ and the solution was concentrated in *vacuo* to give the title compound as a white solid in an 82% yield (4.11 g, 19.2 mmol). Melting point 107-108°C; lit. 102-104°C.[19]

IR (ATR): 3344 (N-H stretch), 1676 (C=O, stretch), 1164 (C-O stretch) cm$^{-1}$.

$[\alpha]_D^{25}$ (deg cm$^3$ g$^{-1}$ dm$^{-1}$) -44.7 (c= 1.0 g cm$^{-3}$ in MeOH), $[\alpha]_D^{25}$ (deg cm$^3$ g$^{-1}$ dm$^{-1}$) literature -42.4 (c=1.0 g cm$^{-3}$ in MeOH).[14]

$^1$H NMR (400 MHz, *CDCl$_3$*) δ ppm: 6.85 (1H, s), 5.40-6.10 (1H, m), 4.35-4.15 (1H, m), 3.55-3.25 (2H, m), 2.40-1.80 (4H, m), 1.45 (9H, s).

HRMS (ESI): $[M+Na]^+$ HRMS found 237.1209, $C_{10}H_{18}N_2O_3Na$ required 237.1210 Data in agreement with the literature[14].

A flask containing Boc-*L*-proline amide (4.02 g, 18.8 mmol) and $NEt_3$ (5.78mL, 41.4 mmol) in THF (60 mL) was cooled to 0°C and stirred. After 30 minutes of stirring, TFAA (3.92 mL, 28.2 mmol) was added, and the reaction continued to be stirred at 0 °C. After 2 hours the reaction was warmed to room temperature and continued to be stirred. After stirring overnight, the reaction was deemed complete by TLC (100% EtOAc ; CAM stain) and the stirring was stopped. The solvent was removed in *vacuo*. The crude yellow oil was redissolved in EtOAc, washed with 2M HCl and extracted with EtOAc (x3) from the HCl wash. The organic layers were combined, washed with saturated $NaHCO_3$ and then with brine. Organic layers were combined, dried over $Na_2SO_4$ and filtered. The solution was concentrated in *vacuo* to give the crude product as orange oil. The crude oil was further purified by column chromatography (gradient from hexane to EtOAc) to give as a pale yellow oil in a 95 % yield (3.51 g, 17.9 mmol).

IR (ATR): 2980, 1694, 1387, 1158 cm$^{-1}$.

$[\alpha]_D^{20}$ –72.77 (c=1.0 mg/mL, MeOH); lit. $[\alpha]_D^{20}$ –91.15 (c=1.3 mg/mL, MeOH).[14]

$^1$H NMR (400 MHz, Chloroform-*d*) δ ppm: 4.60 - 4.40 (1 H, m), 3.58-3.25 (2 H, m) 2.30 – 1.95 (4 H, m), 1.50 - 1.45 (9 H, m).

$^{13}$C NMR (101 MHz, Chloroform-*d*) δ 153.8 and 153.2 (rotamers), 119.2, 81.6 and 81.1 (rotamers), 47.3 and 47.1 (rotamers), 46.1 and 45.8 (rotamers), 31.7 and 30.9 (rotamers), 28.4 and 28.3 (rotamers), 24.7 and 23.9 (rotamers).

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{10}H_{16}N_2NaO_2$ - 219.1104; found: $C_{10}H_{16}N_2NaO_2$ - 219.1102. Data in agreement with the literature.[14]

The flask with Boc-*L*-proline nitrile (1.0 g, 5.1 mmol), TFA (17.00 mL, 229.5 mmol) was added, and the flask was cooled to 0°C. Upon consumption of the starting material (hexane : EtOAc = 8 : 2; CAM stain), *t*-BuOH (0.97 mL, 10.2 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was left stirring overnight. Stirring was stopped and the solvent was removed in *vacuo*. Trituration with di*iso*propyl ether-hexane provided the salt as a yellow solid in a 77 % yield (1.1 g, 3.9 mmol). Melting point 87-89°C; lit. 88-90°C.[14]

IR (ATR): 1661, 1177, 1131 $cm^{-1}$.

$[\alpha]_D^{20}$ –44.36 (c=1.0 mg/mL, DCM); lit. $[\alpha]_D^{25}$ –47.23 (c=1.0 mg/mL, DCM).[14]

$^1$H NMR (400 MHz, Methanol-$d_4$) δ 4.12 (dd, *J* = 8.5, 6.8 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.36 – 3.24 (m, 1H), 2.43 – 2.31 (m, 1H), 2.06 – 1.85 (m, 3H), 1.33 (s, 9H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) δ 167.7, 167.6, 59.7, 52.2, 52.1, 46.4, 30.5, 28.5, 24.7. (TFA signals are absent)

HRMS (ESI) *m/z* $[M + H]^+$ calculated for $C_9H_{19}N_2O$ - 171.1492; found: $C_9H_{19}N_2O$ – 171.1493. Data agree with the literature.[14]

**_t_-Butyl _L_-Proline imidate (3)**

The free *L*-proline imidate **3** was liberated by dissolving the salt (1.0 g, 3.9 mmol) in DCM and stirring over $K_2CO_3$ (2.69 g, 19.5 mmol) for 1 hour before filtering and concentrating in *vacuo*. The crude product was purified by column chromatography (gradient from DCM to MeOH; TLC – DCM : MeOH = 8 : 2 and CAM stain); the free base imidate **3** was obtained as yellow solid in a 62 % yield (0.4 g, 2.4 mmol). Melting point 68-69°C.

IR (ATR): 2965, 1657, 1518, 1454, 1226 $cm^{-1}$.

$[\alpha]_D^{20}$ –51.54 (c=1.0 mg/mL, MeOH).

$^1$H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.40 (br s, 1H), 3.60 (dd, *J* = 8.9, 5.5 Hz, 1H), 2.98 (dt, *J* = 10.3, 6.8 Hz, 1H), 2.86 (dt, *J* = 10.3, 6.4 Hz, 1H), 2.26 (br s, 1H), 2.12 – 2.01 (m, 1H), 1.91 – 1.79 (m, 1H), 1.77 – 1.54 (m, 2H), 1.32 (s, 9H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) δ 174.3, 61.2, 50.2, 47.3, 30.8, 28.8, 26.3.

HRMS (ESI) *m/z* $[M + H]^+$ calculated for $C_9H_{19}N_2O$ - 171.1492; found: $C_9H_{19}N_2O$ – 171.1492. Data agree with the literature.[14]

**General Procedure for the Michael Reaction Catalyzed by Proline Imidate 3**

To a flame dried flask under a $N_2$ atmosphere was added proline imidate **3** (0.025 mmol, 0.1 eq.), benzoic acid (0.025 mmol, 0.1eq) ketone **1** (1.250 mmol, 5 eq.) in 1 mL of toluene and stirred for 15 minutes. After this time nitroalkene **2** (0.250 mmol, 1.0 eq.) was added to the reaction mixture which was stirred at room temperature for 24 hours. The reaction was quenched with 2 mL saturated $NH_4Cl$ solution and extracted with DCM (x3). The organic layers were collected, washed with 0.7M $K_2CO_3$ solution (x1), dried by $Na_2SO_4$, and concentrated to give the crude Michael product.

**(*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]cyclohexanone (4a)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 81% (49.8 mg from 37.3 mg of alkene); white solid; melting point 118-120°C; lit. 128-130°C;[11c] ratio *syn:anti* 27.5:1.0; *ee* (*syn*) 60%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK AS-H column (IPA:Hexane 25:75, flow rate 1 ml/min, λ = 254 nm, 30°C).

IR (ATR): 2977.28, 1706.60, 1550.44, 1379.83, 1130.14, 702.19 $cm^{-1}$.

$[\alpha]_D^{20}$ +14.4 (c=0.58 mg/ml, $CHCl_3$); lit. $[\alpha]_D^{25}$ +19.1 (c=1.0 mg/ml, $CHCl_3$).[11c]

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.39 – 7.22 (m, 3H), 7.22 – 7.08 (m, 2H), 4.93 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.62 (dd, *J* = 12.6, 9.9 Hz, 1H), 3.75 (td, *J* = 10.0, 4.5 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.52 – 2.25 (m, 2H), 2.13 – 2.01 (m, 1H), 1.83 – 1.48 (m, 4H), 1.31 – 1.15 (m, 1H). Data in agreement with the literature.[15a]

Detected *anti* isomer signal: δ 4.02 – 3.97 (m, 1H).[15b]

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 212.1, 135.9, 129.1, 128.3, 127.9, 79.0, 52.6, 44.02, 42.9, 33.3, 28.6, 25.1.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{14}H_{17}NNaO_3$ – 270.1101; found: $C_{14}H_{17}NNaO_3$ – 270.1103.

**(*R*)-2-[(*S*)-Nitro-1-phenylethyl]tetrahydropyran-4-one (4b)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 87% (54.3 mg from 37.3 mg of alkene); white solid; ratio *syn:anti* 10.1:1.0; *ee* (*syn*) 61%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 15:85, flow rate 1 ml/min, λ = 210 nm, 25°C).

IR (ATR): 2977.27, 2831.30, 1711.09, 1551.61, 1380.25, 702.69 $cm^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.37 – 7.26 (m, 3H), 7.19 – 7.14 (m, 2H), 4.92 (dd, *J* = 12.7, 4.6 Hz, 1H), 4.63 (dd, *J* = 12.7, 10.1 Hz, 1H), 4.18 – 4.09 (m, 1H), 3.87 – 3.62 (m, 3H), 3.26 (dd, *J* = 11.6, 8.9 Hz, 1H), 2.92 – 2.82 (m, 1H), 2.71 – 2.61 (m, 1H), 2.55 (dt, *J* = 13.9, 4.0 Hz, 1H). Data in agreement with the literature.[15]

Detected *anti* isomer signals: δ 4.89 – 4.83 (m, 1H), 3.95 (dt, *J* = 8.9, 6.0 Hz, 1H), 3.52 – 3.45 (m, 1H), 2.97 (dt, *J* = 8.6, 5.6 Hz, 1H), 2.52 – 2.43 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 207.5, 136.3, 129.4, 128.4, 128.0, 78.8, 71.7, 69.1, 53.4, 43.1, 41.4.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{13}H_{15}NNaO_4$ – 272.0893; found: $C_{13}H_{15}NNaO_4$ – 272.0893.

**(*S*)-2-[(*S*)-Nitro-1-phenylethyl]-tetrahydrothiopyran-4-one (4c)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 75% (49.9 mg from 37.3 mg of alkene); white solid; ratio *syn:anti* 7.8:1.0; *ee* (*syn*) 71%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 15:85, flow rate 0.95 ml/min, λ = 210 nm, 25°C).

IR (ATR): 2970.77, 2916.50, 1705.81, 1549.81, 1549.56, 1379.93, 701.61 $cm^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.38 – 7.26 (m, 3H), 7.20 – 7.15 (m, 2H), 4.73 (dd, *J* = 12.8, 4.6 Hz, 1H), 4.62 (dd, *J* = 12.8, 9.8 Hz, 1H), 3.97 (td, *J* = 10.2, 4.6 Hz, 1H), δ 3.08 – 3.00 (m, 1H), 3.00 – 2.92 (m, 2H), 2.92 – 2.75 (m, 2H), 2.60 (ddd, *J* = 13.9, 4.1, 1.8 Hz, 1H), 2.44 (dd, *J* = 13.9, 9.4 Hz, 1H). Data (*syn*) in agreement with the literature.[15]

Detected *anti* isomer signals: δ 4.92 – 4.77 (m, 2H), 4.18 – 4.11 (m, 1H), 3.15 – 3.09 (m 1H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 209.6, 136.6, 129.4, 128.4, 128.3, 78.7, 55.1, 44.6, 43.6, 35.2, 31.7.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{13}H_{15}NNaO_3S$ – 288.0665; found: $C_{13}H_{15}NNaO_3S$ – 288.0669.

**(*S*)-2-[(*S*)-Nitro-1-phenylethyl]-*N*-*tert*-butyl oxycarbonate piperidine-4-one (4d)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 71% (61.8 mg from 37.3 mg of alkene); white solid; ratio *syn:anti* 3.8:1.0; ee (*syn*) 53%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 1.3 ml/min, λ = 210 nm, 25 °C)

IR (ATR): 2976.97, 2927.85, 1689.38, 1551.11, 1420.82, 1366.43, 1239.72, 1160.53, 731.30, 701.08$cm^{-1}$.

$^1$H NMR (400 MHz, Chloroform-d) (*syn*): δ 7.36 – 7.22 (m, 3H), 7.22 – 7.14 (m, 2H), 4.91 (dd, J = 12.7, 4.6 Hz, 1H), 4.59 (dd, J = 12.7, 9.8 Hz, 1H), 4.19 (brs, 1H), 3.81 (brs, 2H), 3.29 – 3.05 (m, 1H), 2.88 – 2.60 (m, 2H), 2.57 – 2.39 (m, 2H), 1.60 – 1.08 (m, 9H). Data in agreement with the literature.[15]

Detected *anti* isomer signals: δ 4.96 – 4.82 (m, 1H), 3.45 – 3.33 (m, 1H), 3.29 – 3.05 (m, 1H), 2.35 (t, J = 6.4 Hz, 2H).

$^{13}$C NMR (101 MHz, Chloroform-d) (*syn*): δ 208.5, 154.2, 136.6, 129.3, 129.1, 128.3, 128.2, 128.1, 80.8, 79.0, 44.3, 41.9, 41.9, 40.9, 28.3.

HRMS (ESI) m/z [M + Na]+ calculated for $C_{18}H_{24}N_2NaO_5$ – 371.1577; found: $C_{18}H_{24}N_2NaO_5$ – 371.1586.

**(*R*)-2-[(*S*)-Nitro-1-phenylethyl]cyclobutanone (4e)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 27% (14.8 mg from 37.3 mg of alkene); yellow oil; ratio *syn*:*anti* 2.4:1.0; ee (*syn*) 37%, ee. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK AS-H column (IPA:Hexane 25:75, flow rate 0.7 ml/min, λ = 210 nm, 25 °C).

IR (ATR): 2923.30, 1774.51, 1550.51, 1379.41, 1086.02, 701.54 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-d) (*syn*): δ 7.38 – 7.26 (m, 3H), 7.21 – 7.15 (m, 2H), 5.06 (dd, J = 12.8, 4.6 Hz, 1H), 4.63 (dd, J = 12.8, 9.9 Hz, 1H), 3.76 – 3.65 (m, 1H), 3.65 – 3.52 (m, 1H), 3.15 – 2.87 (m, 2H), 2.10 – 1.98 (m, 1H), 1.78 – 1.60 (m, 1H). Data (*syn*) in agreement with the literature.[11b]

*Anti* isomer signals: δ 7.38 – 7.26 (m, 3H), 7.21 – 7.15 (m, 2H), 4.92 – 4.76 (m, 2H), 3.76 – 3.65 (m, 2H), 3.15 – 2.87 (m, 1H), 2.68 – 2.57 (m, 1H), 2.22 – 2.10 (m, 1H), 1.78 – 1.60 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-d) (*syn*): δ 208.7, 137.4, 129.2, 128.3, 127.7, 78.3, 61.1, 44.6, 44.4, 15.9.

Detected *anti* isomer signals: δ 136.5, 129.1, 128.3, 77.7, 61.5, 45.1, 44.3, 14.4.

HRMS (ESI) m/z [M + Na]+ calculated for $C_{12}H_{13}NNaO_3$ – 242.0788; found: $C_{12}H_{13}NNaO_3$ – 242.0786.

**(*R*)-2-[(*S*)-Nitro-1-phenylethyl]cyclopentanone (4f)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 21% (12.2 mg from 37.3 mg of alkene); white solid; ratio *syn:anti* 6.0:1.0; *ee* (*syn*) 60%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK AS-H column (IPA:Hexane 25:75, flow rate 1 ml/min, λ = 210 nm, 25°C).

IR (ATR): 2967.49, 1732.30, 1549.98, 1379.68, 1154.87, 702.35 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.36 – 7.21 (m, 3H), 7.21 – 7.11 (m, 2H), 5.33 (dd, *J* = 12.9, 5.6 Hz, 1H), 4.70 (dd, *J* = 12.9, 9.8 Hz, 1H), 3.68 (td, *J* = 9.5, 5.6 Hz, 1H), 2.45 – 2.29 (m, 2H), 2.18 – 2.06 (m, 1H), 1.98 – 1.77 (m, 2H), 1.77 – 1.62 (m, 1H), 1.54 – 1.39 (m, 1H). Data (*syn*) in agreement with the literature.[11b]

Detected *anti* isomer signals: δ 5.01 (d, *J* = 7.8 Hz, 2H), 3.85 – 3.78 (m, 1H), 2.54 – 2.46 (m, 1H), 2.29 – 2.22 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 218.6, 137.8, 129.0, 128.1, 128.0, 78.4, 50.6, 44.3, 38.8, 28.4, 20.4.

HRMS (ESI) *m/z* [M + Na]$^+$ calculated for $C_{13}H_{15}NNaO_3$ – 256.0944; found: $C_{13}H_{15}NNaO_3$ – 256.0942.

**(*R*)-2-Methyl-(*S*)-3-phenyl-4-nitrobutanal (4h)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 85% (44.0 mg from 37.3 mg of alkene); yellow oil; ratio *syn:anti* 4.6:1.0 (epimerization over time *syn* to *anti*); *ee* (*syn*) 84%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 1.3 ml/min, λ = 210 nm, 25°C).

IR (ATR): 2974.90, 2730.6, 1722.71, 1551.14, 1379.6, 702.48 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 9.70 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.22 – 7.11 (m, 2H), 4.84 – 4.71 (m, 1H), 4.71 – 4.62 (m, 1H), 3.80 (td, *J* = 9.1, 5.7 Hz, 1H), 2.86 – 2.70 (m, 1H), 0.98 (d, *J* = 7.2 Hz, 3H). Data (*syn*) in agreement with the literature.[11e]

*Anti* isomer signals: δ 9.52 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.22 – 7.11 (m, 2H), 4.84 – 4.71 (m, 2H), 3.80 (td, *J* = 9.1, 5.7 Hz, 1H), 2.86 – 2.70 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 2H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 202.39, 136.64, 129.19, 128.27 & 128.24 *syn/anti*, 128.17, 78.21, 48.53, 44.12, 12.23..

Detected *anti* isomer signals: δ 202.5, 137.0, 129.2, 128.3 & 128.2 *syn/anti*, 48.8, 44.9, 11.8.

HRMS (ESI) *m/z* [M + Na]$^+$ calculated for $C_{11}H_{13}NNaO_3$ – 230.0788; found: $C_{11}H_{13}NNaO_3$ – 230.0788.

**(*R*)-2-[(*S*)-2-Nitro-1-*para*-methoxyphenylethyl]cyclohexanone (4j)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 75% (51.9 mg from 44.8 mg of alkene); white solid; ratio *syn:anti* 10.0:1.0; *ee* (*syn*) 43%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 10:90, flow rate 0.5 ml/min, λ = 254 nm, 25 °C).

IR (ATR): 2940.52, 2862.98, 1706.24, 1550.11, 1514.27, 1251.39, 831.82 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.11 – 7.02 (m, 2H), 6.87 – 6.79 (m, 2H), 4.90 (dd, *J* = 12.4, 4.6 Hz, 1H), 4.57 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.77 (s, 3H), 3.70 (td, *J* = 9.9, 4.6 Hz, 1H), 2.69 – 2.58 (m, 1H), 2.51 – 2.31 (m, 2H), 2.11 – 2.01 (m, 1H), 1.82 – 1.47 (m, 4H), 1.29 – 1.14 (m, 1H). Data (*syn*) in agreement with the literature.[11d]

Detected *anti* isomer signals: δ 7.19 – 7.13 (m, 2H), 6.86 – 6.81 (m, 2H), 4.79 (dd, *J* = 12.7, 9.7 Hz, 1H), 3.93 – 3.87 (m, 1H), 1.43 – 1.34 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 212.2, 159.1, 129.6, 129.3, 114.4, 79.2, 55.3, 52.8, 43.3, 42.8, 33.2, 28.6, 25.1.

HRMS (ESI) *m/z* [M + Na]$^+$ calculated for $C_{15}H_{19}NNaO_4$ – 300.1206; found: $C_{15}H_{19}NNaO_4$ – 300.1210.

**(*R*)-2-[(*S*)-2-Nitro-1-*ortho*-chlorophenylethyl]cyclohexanone (4k)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 96% (67.4 mg from 45.9 mg of alkene); white solid; melting point 67-69°C lit. 64-66°C[11c]; ratio *syn:anti* 20.0:1.0; *ee* (*syn*) 38%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 10:90, flow rate 1 ml/min, λ = 254 nm, 25 °C).

IR (ATR): 2940.72, 2862.97, 1706.27, 1550.36, 1379.07, 754.95cm$^{-1}$.

$[\alpha]_D^{20}$ +15.30 (c=0.58 mg/ml, $CHCl_3$); lit. $[\alpha]_D^{25}$ +45.3 (c= 1.0 mg/ml, $CHCl_3$).[11c]

$^1$H NMR (400 MHz, Chloroform-d) (*syn*): δ 7.39 – 7.34 (m, 1H), 7.30 – 7.15 (m, 3H), 4.95 – 4.83 (m, 2H), 4.32 – 4.22 (m, 1H), 2.97 – 2.84 (m, 1H), 2.50 – 2.32 (m, 2H), 2.14 – 2.04 (m, 1H), 1.85 – 1.51 (m, 4H), 1.44 – 1.17 (m, 1H). Data (*syn*) in agreement with the literature.[11b]

Detected *anti* isomer signal: δ 4.69 – 4.62 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-d) (*syn*): δ 211.8, 135.5, 134.6, 130.5, 129.0, 127.5, 77.3, 51.8, 42.9, 33.2, 28.6, 25.4.

HRMS (ESI) m/z [M + Na]+ calculated (as 3:1) for $C_{14}H_{16}{}^{35}ClNNaO_3$ – 304.0711 and $C_{14}H_{16}{}^{37}ClNNaO_3$ – 306.0681; found (as 3:1): $C_{14}H_{16}{}^{35}ClNNaO_3$ – 304.0709 and $C_{14}H_{16}{}^{37}ClNNaO_3$ – 306.0685.

**(*R*)-2-[(*S*)-2-Nitro-1-(pyridine-3-yl)ethyl]cyclohexanone (4l)**

Flash columned with a gradient from neat hexane to EtOAc; isolated yield – 94% (58.3 mg from 37.5 mg of alkene); yellow solid; ratio *syn:anti* 5.1:1.0; *ee* (*syn*) 36%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 20:80, flow rate 0.75 ml/min, λ = 254 nm, 25°C).

IR (ATR): 2941.92, 2863.77, 1705.77, 1549.90, 1428.42, 1379.16, 1130.88, 716.55 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 8.52 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.46 (d, *J* = 2.3 Hz, 1H), 7.53 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.29 – 7.25 (m, 1H), 4.94 (dd, *J* = 12.9, 4.6 Hz, 1H), 4.68 (dd, *J* = 12.9, 9.9 Hz, 1H), 3.80 (td, *J* = 9.6, 4.6 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.53 – 2.32 (m, 2H), 2.14 – 2.05 (m,

1H), 1.85 – 1.50 (m, 4H), 1.25 (qd, *J* = 12.7, 3.5 Hz, 1H). Data (*syn*) in agreement with the literature.[11d]

Detected *anti* isomer signals: δ 8.54 – 8.48 (m, 2H), 7.67 (dt, *J* = 7.9, 1.9 Hz, 1H), 4.91 – 4.83 (m, 2H), 3.94 – 3.88 (m 1H), δ 2.80 – 2.72 (m, 1H), 2.35 – 2.23 (m, 2H), 1.97 – 1.87 (m, 1H), 1.43 – 1.31 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 211.2, 150.0, 149.4, 135.8, 133.6, 123.8, 78.2, 52.3, 42.8, 41.7, 33.3, 28.4, 25.2.

Detected *anti* isomer signals: δ 149.13, 136.23, 123.66, 53.33, 42.48, 41.53, 30.77, 27.39.

HRMS (ESI) *m/z* [M + H]$^+$ calculated for $C_{13}H_{17}N_2O_3$ – 249.1234; found: $C_{13}H_{17}N_2O_3$ – 249.1233.

**(*R*)-2-[(*R*)-2-Nitro-1-(thiophen-2-yl)ethyl]cyclohexanone (4m)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 71% (44.9 mg from 38.8 mg of alkene); yellow solid; ratio *syn:anti* 5.2:1.0; *ee* (*syn*) 56%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 10:90, flow rate 1 ml/min, λ = 254 nm, 25°C).

IR (ATR): 2939.28, 2863.07, 1705.30, 1550.94 1378.52, 1128.88, 705.58 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.20 (dd, *J* = 5.2, 1.3 Hz, 1H), 6.92 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.86 (dd, *J* = 3.5, 1.3 Hz, 1H), 4.88 (dd, *J* = 12.7, 4.7 Hz, 1H), 4.64 (dd, *J* = 12.7, 9.4 Hz, 1H), 4.12 (td, *J* = 9.1, 4.8 Hz, 1H), 2.71 – 2.61 (m, 1H), 2.51 – 2.24 (m, 2H), 2.18 – 2.02 (m, 1H), 1.95 – 1.78 (m, 2H), 1.73 – 1.57 (m, 2H), 1.47 – 1.21 (m, 1H). Data (*syn*) in agreement with the literature.[17]

Detected *anti* isomer signals: δ 7.19 (m, 1H), 4.92 – 4.75 (m, 2H), 4.23 – 4.17 (m, 1H), 2.79 – 2.71 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 211.3, 140.6, 127.0, 126.8, 125.1, 79.3, 53.5, 42.7, 39.5, 32.9, 28.4, 25.2.

Detected *anti* isomer signals: δ 126.88, 125.35, 78.18, 53.56, 42.38, 39.60, 30.77, 27.28.

HRMS (ESI) *m/z* [M + Na]$^+$ calculated for $C_{12}H_{15}NNaO_3S$ – 276.0665; found: $C_{12}H_{15}NNaO_3S$ – 276.0669.

**(*R*)-2-[(*S*)-2-Nitro-1-*ortho*-chlorophenylethyl]cyclobutanone (4n)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 50% (31.6 mg from 45.9 mg of alkene); yellow oil; ratio *syn:anti* 1.6:1.0; *ee* (*syn*) 15%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 0.7 ml/min, λ = 210 nm, 25°C).

IR (ATR): 2921.86, 1774.29, 1550.01, 1378.25, 1083.26, 1038.99, 756.18 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.47 – 7.35 (m, 1H), 7.30 – 7.15 (m, 3H), 5.04 (dd, *J* = 12.9, 4.6 Hz, 1H), 4.92 – 4.80 (m, 1H), 4.29 – 4.19 (m, 1H), 3.88 – 3.76 (m, 1H), 3.19 – 2.92 (m, 2H), 2.13 – 1.99 (m, 1H), 1.79 – 1.60 (m, 1H). Data (*syn*) in agreement with the literature.[11b]

*Anti* isomer signals: δ 7.47 – 7.35 (m, 1H), 7.30 – 7.15 (m, 3H), 4.92 – 4.80 (m, 2H), 4.40 (q, *J* = 7.4 Hz, 1H), 3.88 – 3.76 (m, 1H), 3.19 – 2.92 (m, 1H), 2.76 – 2.63 (m, 1H), 2.27 – 2.16 (m, 1H), 1.79 – 1.60 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 208.4, 134.7, 134.2, 130.5, 129.4 & 129.3 *syn/anti*, 128.4, 127.7 & 127.6 *syn/anti*, 76.6, 60.6, 45.2, 44.5, 16.03.

Detected *anti* isomer signals: δ 208.17, 134.58, 130.38, 129.35 & 129.32 *syn/anti*, 127.66 & 127.60 *syn/anti*, 60.19, 14.72.

HRMS (ESI) *m/z* [M + Na]$^+$ calculated (as 3:1) for $C_{12}H_{12}{}^{35}ClNNaO_3$ – 276.0398 and $C_{12}H_{12}{}^{37}ClNNaO_3$ – 278.0368; found (as 3:1): $C_{12}H_{12}{}^{35}ClNNaO_3$ – 276.0401 and $C_{12}H_{12}{}^{37}ClNNaO_3$ – 278.0377.

**(*R*)-2-Methyl-(*R*)-3-thiophen-2-yl-4-nitrobutanal (4o)**

Flash columned with a gradient from neat hexane to $Et_2O$; isolated yield – 65% (34.6 mg from 38.8 mg of alkene); yellow oil; ratio *syn:anti* 3.7:1.0; *ee* (*syn*) 81.8%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 1.3 ml/min, λ = 210 nm, 25°C).

IR (ATR): 2973.65, 2730.8, 1722.75, 1553.38, 1379.57, 706.16 cm$^{-1}$.

$^1$H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 9.68 (s, 1H), 7.25 – 7.20 (m, 1H), 6.98 – 6.85 (m, 2H), 4.81 – 4.59 (m, 2H), 4.27 – 4.19 (m, 1H), 2.87 – 2.72 (m, 1H), 1.11 (d, *J* = 7.4 Hz, 3H). Data (*syn*) in agreement with the literature.[18]

*Anti* isomer signals: δ 9.60 (s, 1H), 7.25 – 7.20 (m, 1H), 6.98 – 6.85 (m, 2H), 4.81 – 4.59 (m, 2H), 4.19 – 4.12 (m, 1H), 2.87 – 2.72 (m, 1H), 1.25 (d, *J* = 7.4 Hz, 3H).

$^{13}$C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 201., 138.9, 127.2, 126.9, 125.4, 78.5, 48.9, 39.5, 11.6.

*Anti* isomer signals: δ 202.14, 139.25, 127.28, 126.90, 125.53, 78.15, 49.05, 40.17, 11.88.

HRMS (ESI) *m/z* [M + Na]$^+$ calculated for $C_9H_{11}NNaO_3S$ – 236.0352; found: $C_9H_{11}NNaO_3S$ – 236.0362.

## Funding Information

Click here to insert sources of funding, grant numbers, etc. Do not repeat the same in the acknowledgment.

## Acknowledgment

We thank The Wild Fund, University of York for funding (B.S.)

## Supporting Information

YES (this text will be updated with links prior to publication)

## Primary Data

https://doi.org/10.15124/207e9639-5f06-4eea-af9c-4ded13054afa

## Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

# Amino Imidate-Catalyzed Asymmetric Michael Reactions of Ketones and Nitroalkenes

*Bohdan Sosunovych, Alexander J. Brown and Paul A. Clarke**

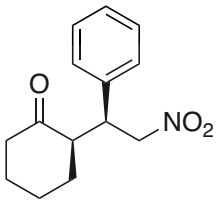


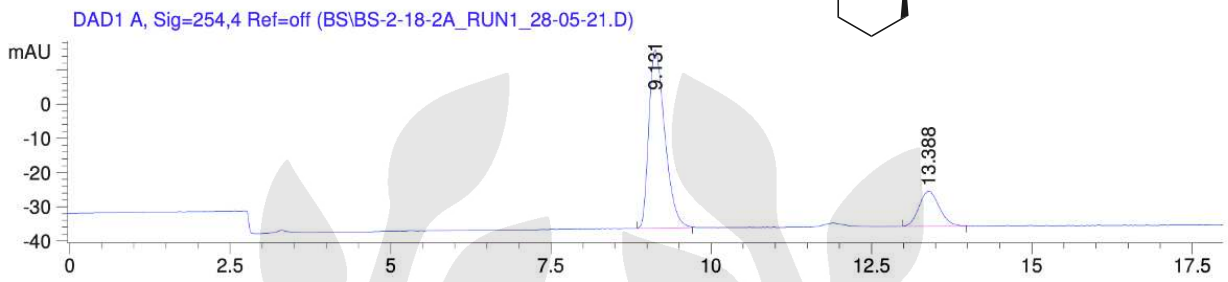


**Contents**

## HPLC Data

HPLC trace of enantioenriched **4a**



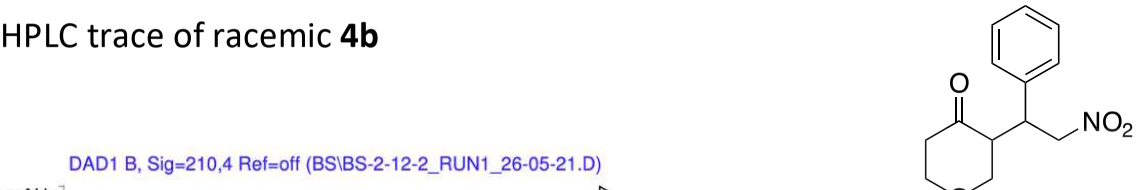



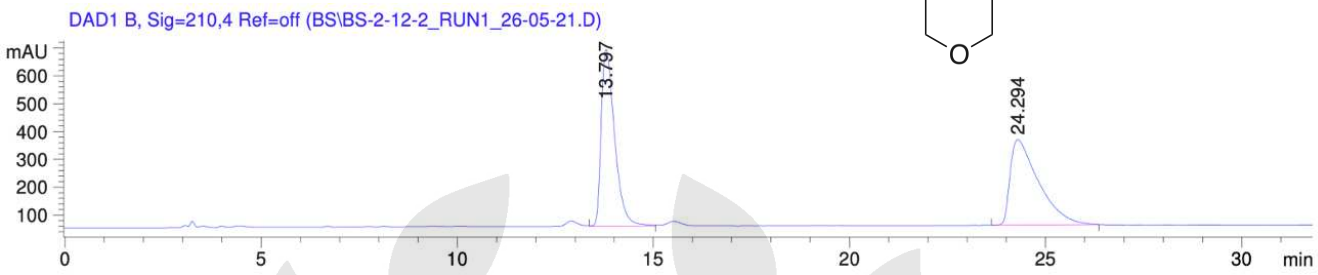

Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.131 | BB | 0.2711 | 906.64490 | 52.06992 | 80.1737 |
| 2 | 13.388 | BB | 0.3432 | 224.20638 | 10.24839 | 19.8263 |
| Totals : | | | | 1130.85127 | 62.31831 | |

*Anti* isomer traces were not detected.
This was compared to the reported racemic HPLC data in
A. Lu, P. Gao, Y. Wu, Y. Wang, Z. Zhou, C. Tang, *Org. Biomol. Chem.,* **2009**, *7*, 3141.

HPLC trace of racemic **4b**



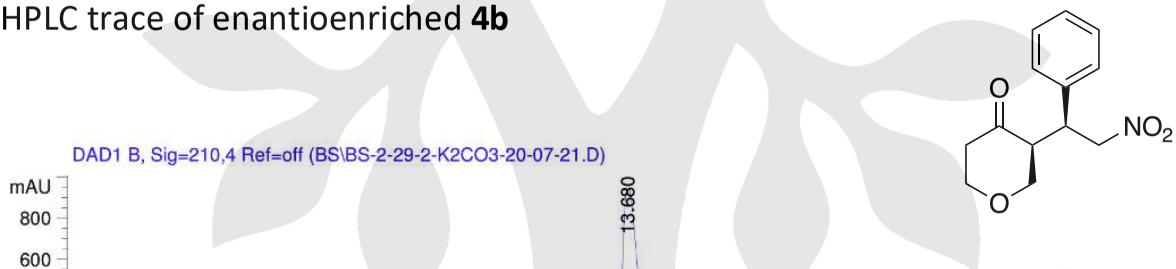



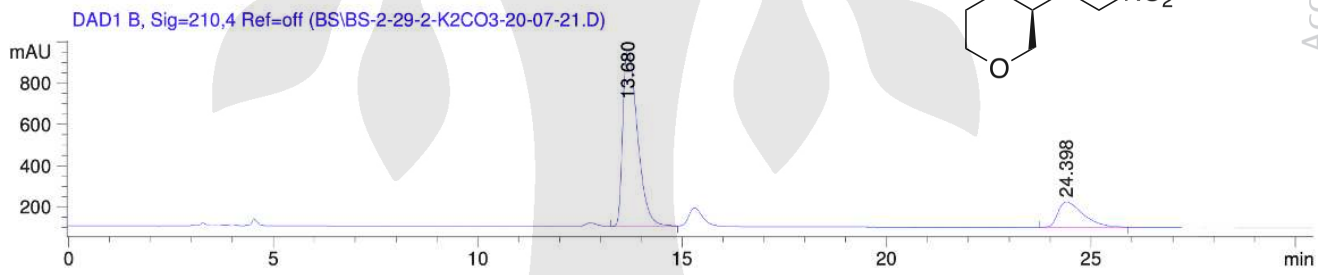

Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 13.797 | VB | 0.3643 | 1.51483e4 | 634.98511 | 49.4392 |
| 2 | 24.294 | BB | 0.7056 | 1.54920e4 | 307.60867 | 50.5608 |
| Totals : | | | | 3.06403e4 | 942.59378 | |

Retention time of minor *anti* isomer traces: 12.9 and 15.5 minutes.

HPLC trace of enantioenriched **4b**

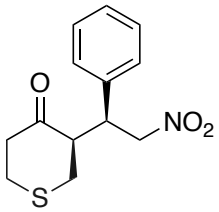


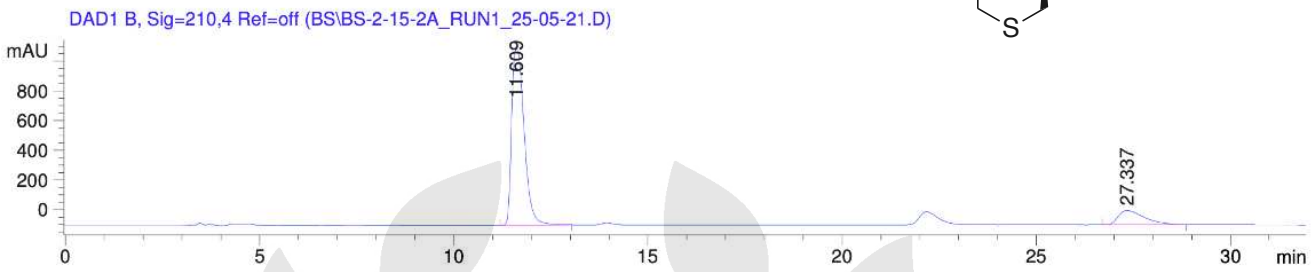




Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 13.680 | VB | 0.3872 | 2.15790e4 | 858.54150 | 80.3249 |
| 2 | 24.398 | BB | 0.6524 | 5285.64746 | 123.23447 | 19.6751 |
| Totals : | | | | 2.68646e4 | 981.77598 | |

HPLC trace of enantioenriched **4c**



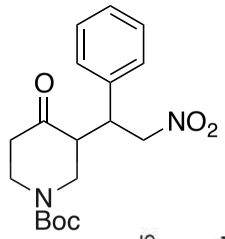

Signal 2: DAD1 B, Sig=210,4 Ref=off

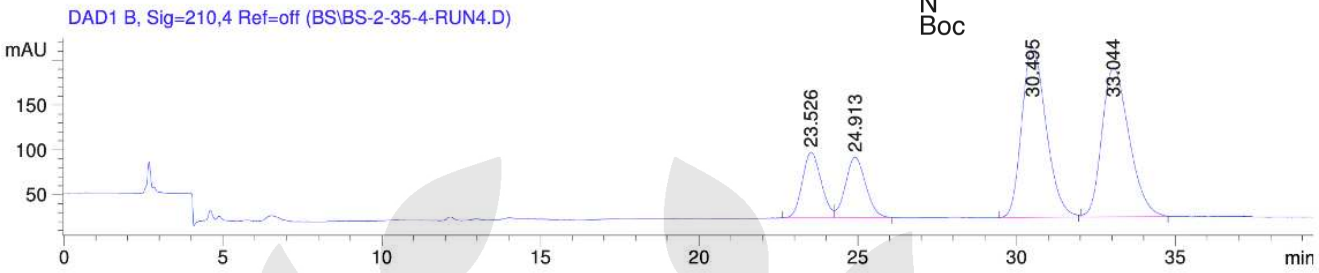
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 11.609 | BB | 0.3533 | 2.65987e4 | 1187.68689 | 85.6685 |
| 2 | 27.337 | BB | 0.6714 | 4449.70117 | 95.88362 | 14.3315 |
| Totals : | | | | 3.10484e4 | 1283.57051 | |

Retention time of minor *anti* isomer traces: 14.0 and 22.3 minutes.

This was compared to the reported racemic HPLC data in M. Freund, S. Schenker, and S.B. Tsogoeva, *Org. Biomol. Chem.,* **2009**, *7*, 4279.

HPLC trace of racemic **4d**



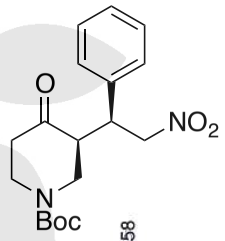



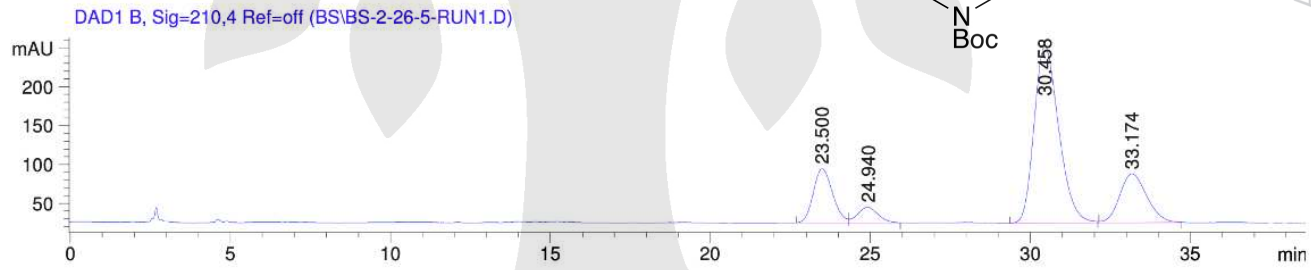

Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 23.526 | BV | 0.6031 | 3033.95068 | 73.27061 | 11.6387 |
| 2 | 24.913 | VB | 0.6281 | 2994.60425 | 67.69376 | 11.4878 |
| 3 | 30.495 | BB | 0.7704 | 1.01300e4 | 189.87624 | 38.8605 |
| 4 | 33.044 | BB | 0.8544 | 9909.09570 | 166.48235 | 38.0130 |
| Totals : | | | | 2.60677e4 | 497.32295 | |

Retention time of minor *anti* isomer traces: 23.5 and 24.9 minutes.

HPLC trace of enantioenriched **4d**

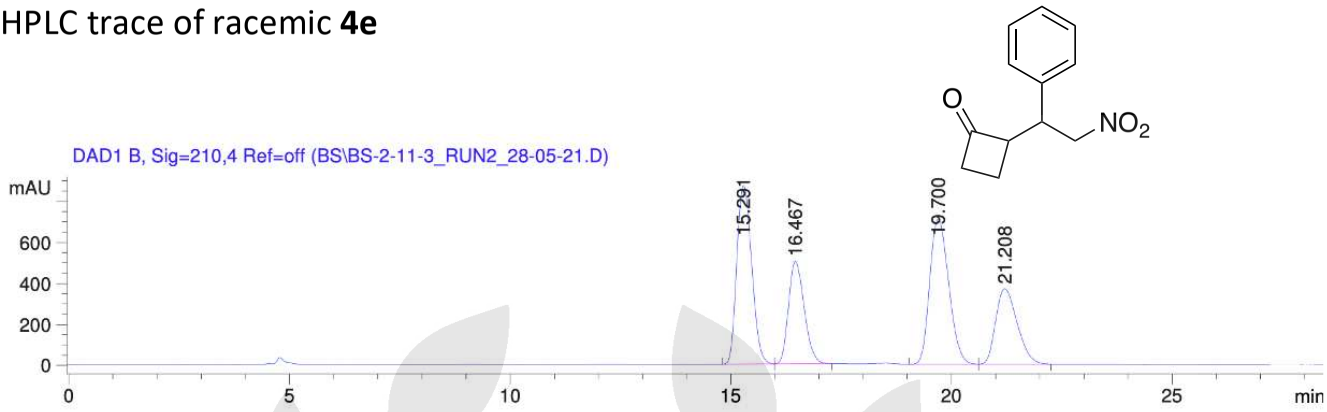



Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 23.500 | BV | 0.6125 | 2911.44336 | 69.53360 | 14.8227 |
| 2 | 24.940 | VV | 0.5483 | 886.20184 | 19.94725 | 4.5118 |
| 3 | 30.458 | BB | 0.8225 | 1.21469e4 | 226.94003 | 61.8422 |
| 4 | 33.174 | BB | 0.7653 | 3697.23218 | 62.75798 | 18.8233 |
| Totals : | | | | 1.96418e4 | 379.17887 | |

HPLC trace of racemic **4e**

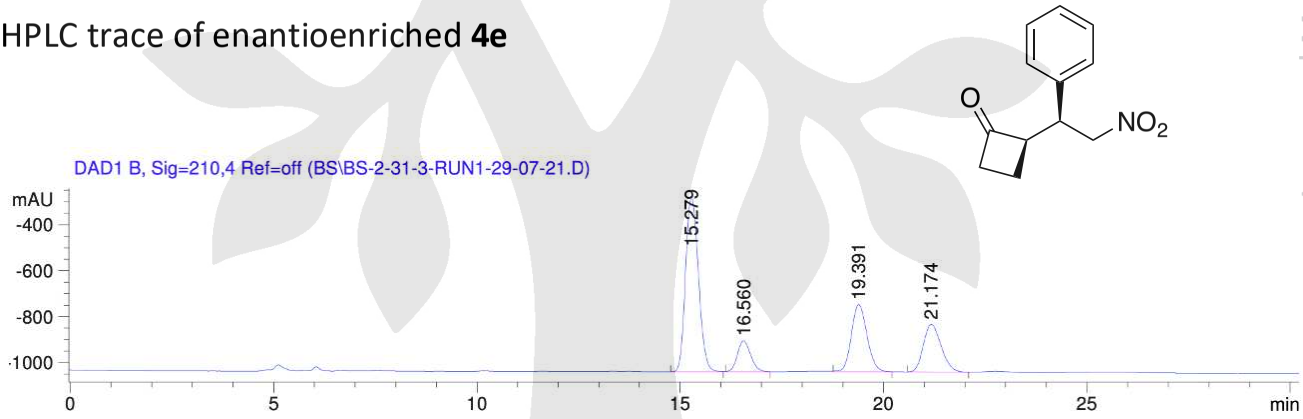



Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 15.291 | BV | 0.3716 | 2.04112e4 | 870.41644 | 30.7447 |
| 2 | 16.467 | VB | 0.3846 | 1.23562e4 | 499.51392 | 18.6117 |
| 3 | 19.700 | VV | 0.4673 | 2.11921e4 | 707.84137 | 31.9210 |
| 4 | 21.208 | VB | 0.5282 | 1.24298e4 | 367.83472 | 18.7226 |
| Totals : | | | | 6.63894e4 | 2445.60645 | |

Retention time of minor *anti* isomer traces: 16.5 and 21.2 minutes.

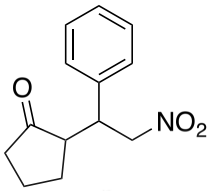
HPLC trace of enantioenriched **4e**

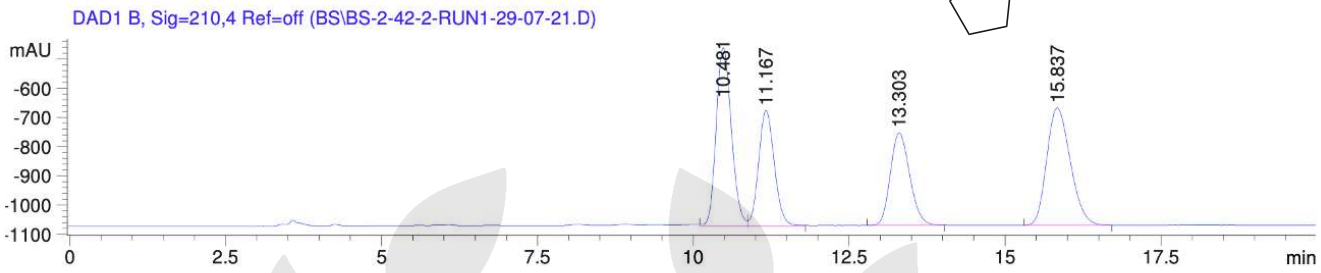



Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 15.279 | BB | 0.3498 | 1.67807e4 | 759.43610 | 49.4399 |
| 2 | 16.560 | BB | 0.3459 | 3044.25562 | 134.57545 | 8.9691 |
| 3 | 19.391 | BB | 0.4191 | 7799.30322 | 292.49927 | 22.9786 |
| 4 | 21.174 | BB | 0.4796 | 6317.36621 | 207.29028 | 18.6124 |
| Totals : | | | | 3.39416e4 | 1393.80110 | |

HPLC trace of racemic **4f**



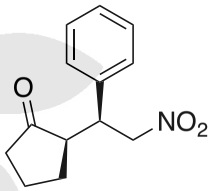



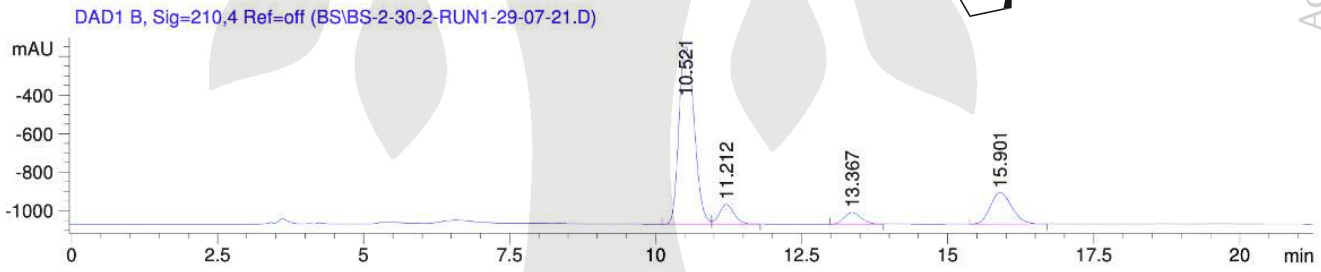

Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 10.481 | VV | 0.2652 | 1.02835e4 | 608.53192 | 29.7616 |
| 2 | 11.167 | VB | 0.2707 | 6840.10156 | 393.77805 | 19.7960 |
| 3 | 13.303 | BB | 0.3383 | 6848.79980 | 316.64307 | 19.8212 |
| 4 | 15.837 | BB | 0.4113 | 1.05805e4 | 401.63190 | 30.6212 |
| Totals : | | | | 3.45529e4 | 1720.58493 | |

Retention time of minor *anti* isomer traces: 11.2 and 13.3 minutes.

HPLC trace of enantioenriched **4f**

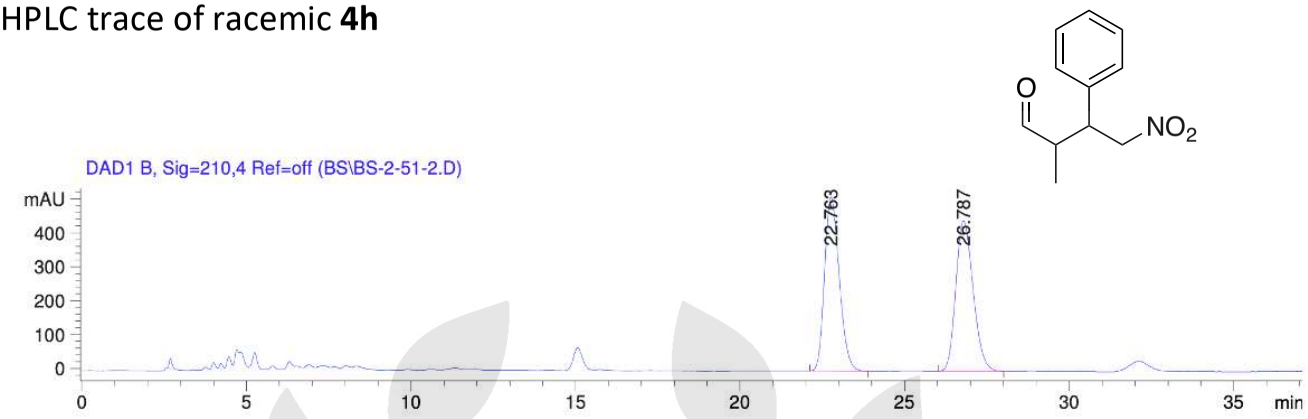



Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 10.521 | BV | 0.2899 | 1.66797e4 | 918.52490 | 69.6380 |
| 2 | 11.212 | VB | 0.2734 | 1794.26526 | 101.89684 | 7.4911 |
| 3 | 13.367 | BV | 0.3220 | 1272.81470 | 60.87047 | 5.3140 |
| 4 | 15.901 | BB | 0.3965 | 4205.24756 | 163.29239 | 17.5570 |
| Totals : | | | | 2.39520e4 | 1244.58460 | |

HPLC trace of racemic **4h**

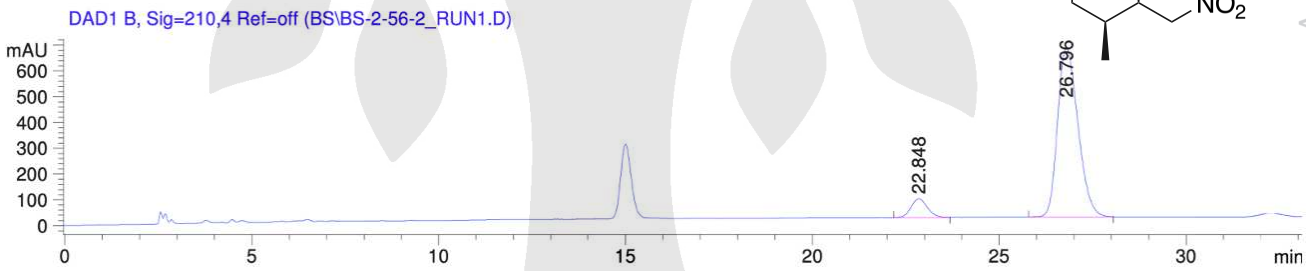



Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 22.763 | BB | 0.4857 | 1.60160e4 | 513.77661 | 49.5807 |
| 2 | 26.787 | BB | 0.5698 | 1.62868e4 | 444.20007 | 50.4193 |
| Totals : | | | | 3.23028e4 | 957.97668 | |

Retention time of minor *anti* isomer traces: 15.1 and 32.1 minutes.

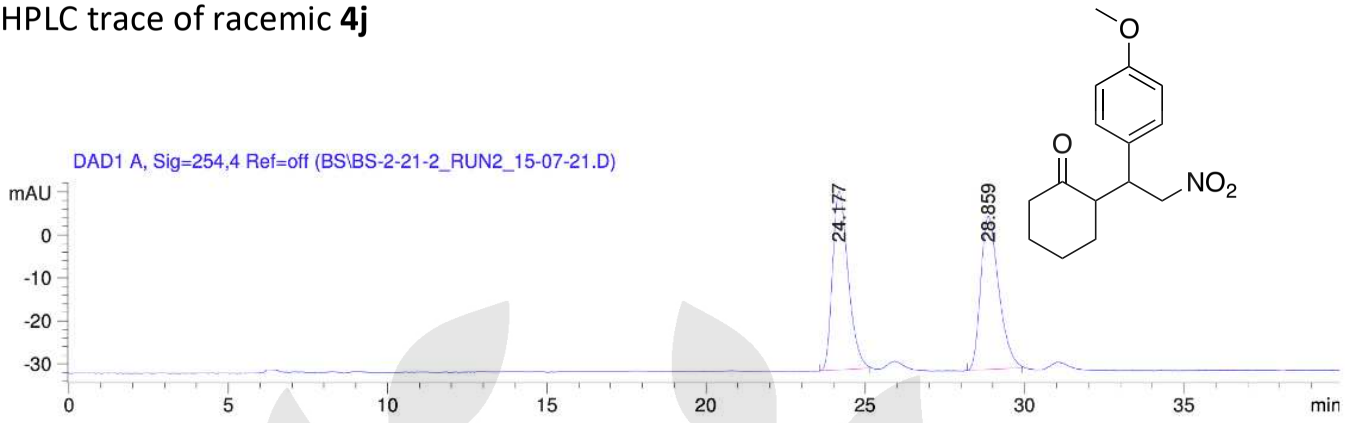
HPLC trace of enantioenriched **4h**




Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 22.848 | BB | 0.4627 | 2197.29102 | 72.68048 | 8.1448 |
| 2 | 26.796 | BB | 0.5955 | 2.47807e4 | 654.79443 | 91.8552 |
| Totals : | | | | 2.69780e4 | 727.47491 | |

HPLC trace of racemic **4j**

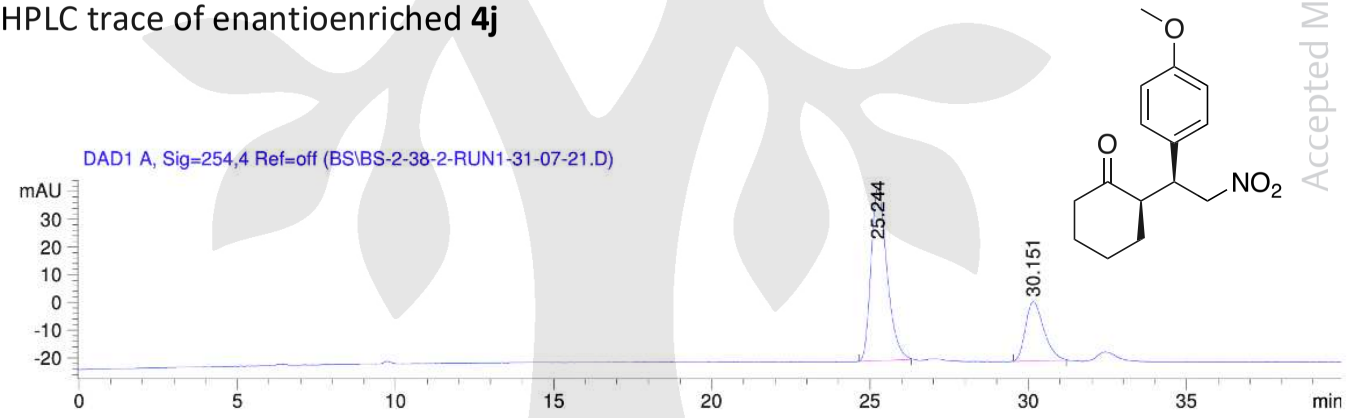



Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 24.177 | BB | 0.5221 | 1421.80518 | 41.45721 | 50.2136 |
| 2 | 28.859 | BB | 0.6023 | 1409.70728 | 35.57922 | 49.7864 |
| Totals : | | | | 2831.51245 | 77.03643 | |

Retention time of minor *anti* isomer traces: 25.9 and 31.1 minutes.

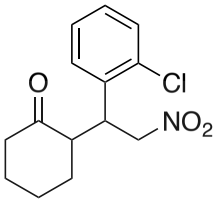
HPLC trace of enantioenriched **4j**

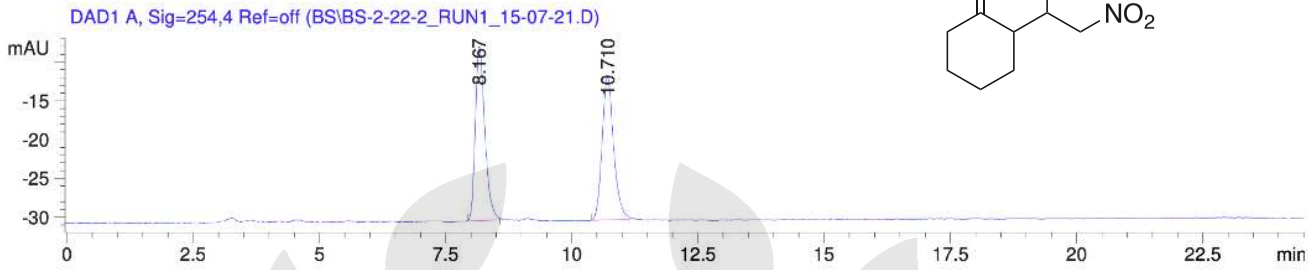



Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 25.244 | BB | 0.5275 | 2188.70923 | 62.05999 | 71.6411 |
| 2 | 30.151 | BB | 0.5460 | 866.39148 | 21.41722 | 28.3589 |
| Totals : | | | | 3055.10071 | 83.47721 | |

HPLC trace of racemic **4k**



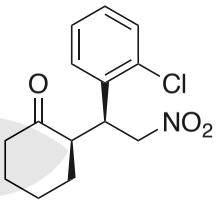



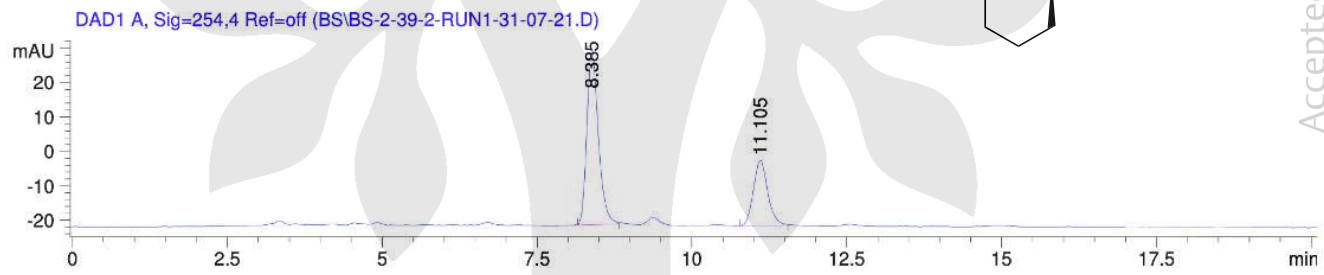

Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.167 | BB | 0.1992 | 294.93860 | 22.46553 | 50.1633 |
| 2 | 10.710 | BB | 0.2454 | 293.01840 | 18.44093 | 49.8367 |
| Totals : | | | | 587.95700 | 40.90646 | |

*Anti* isomer traces were not detected.

HPLC trace of enantioenriched **4k**

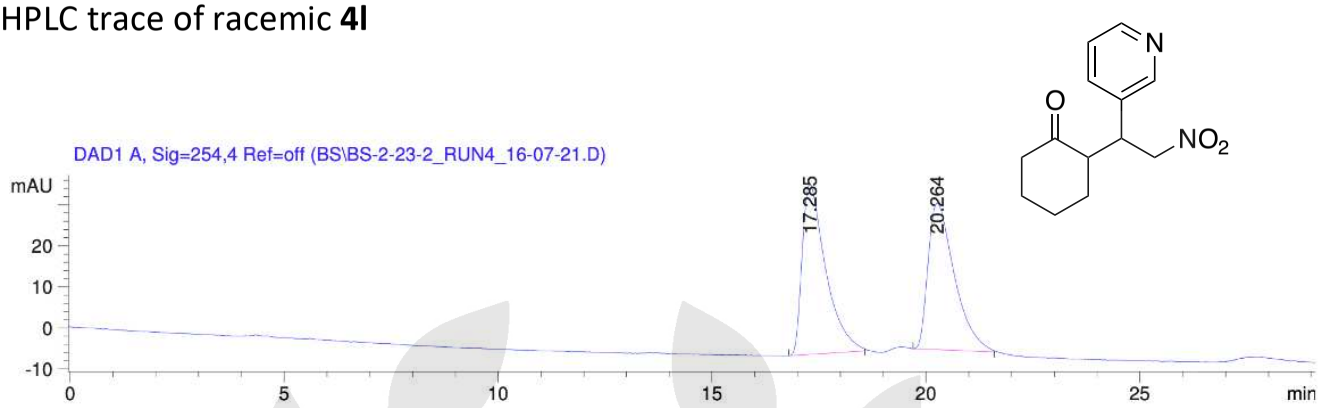



Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.385 | BB | 0.1994 | 671.00269 | 51.03154 | 68.7619 |
| 2 | 11.105 | BB | 0.2493 | 304.83170 | 18.98849 | 31.2381 |
| Totals : | | | | 975.83438 | 70.02002 | |

HPLC trace of racemic **4l**





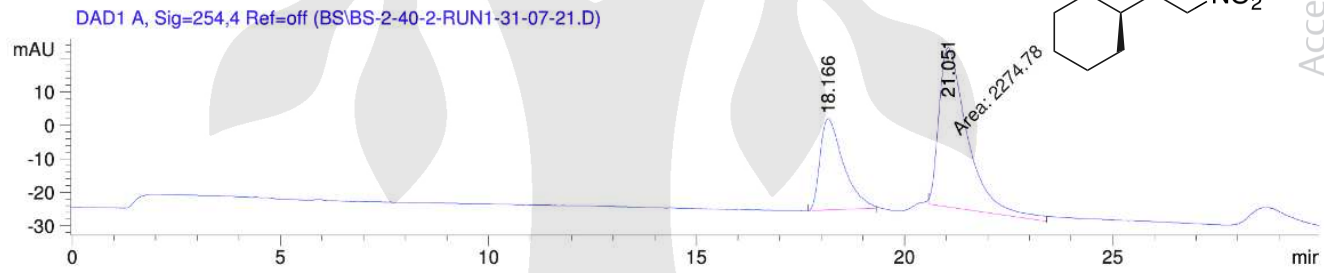


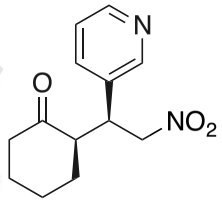
Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 17.285 | BB | 0.5638 | 1594.28320 | 41.53807 | 50.9514 |
| 2 | 20.264 | BB | 0.6109 | 1534.74548 | 35.74903 | 49.0486 |
| Totals : | | | | 3129.02869 | 77.28710 | |

Retention time of minor *anti* isomer traces: 19.4 and 27.8 minutes.

HPLC trace of enantioenriched **4l**

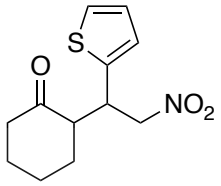


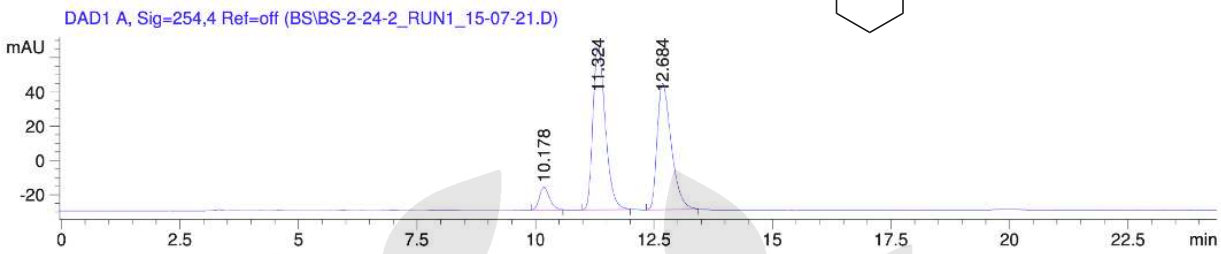




Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 18.166 | BB | 0.5533 | 1059.40222 | 27.26358 | 31.7740 |
| 2 | 21.051 | MM | 0.7966 | 2274.78198 | 47.59598 | 68.2260 |
| Totals : | | | | 3334.18420 | 74.85957 | |

HPLC trace of racemic **4m**



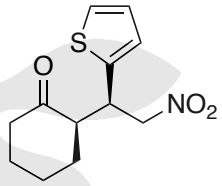



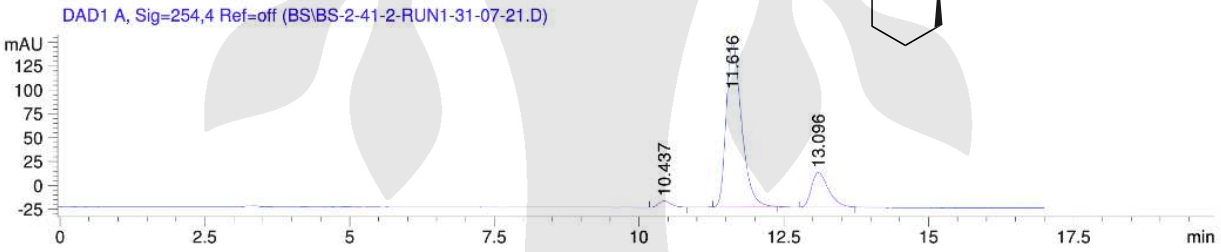

Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 10.178 | BB | 0.2287 | 204.35374 | 13.49066 | 5.8972 |
| 2 | 11.324 | BB | 0.2814 | 1735.22485 | 95.76899 | 50.0746 |
| 3 | 12.684 | BB | 0.3175 | 1525.70239 | 73.69756 | 44.0282 |
| Totals : | | | | 3465.28099 | 182.95722 | |

Retention time of minor *anti* isomer traces: 10.2 and 11.3 (overlapped) minutes.

HPLC trace of enantioenriched **4m**

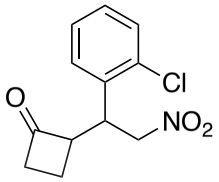


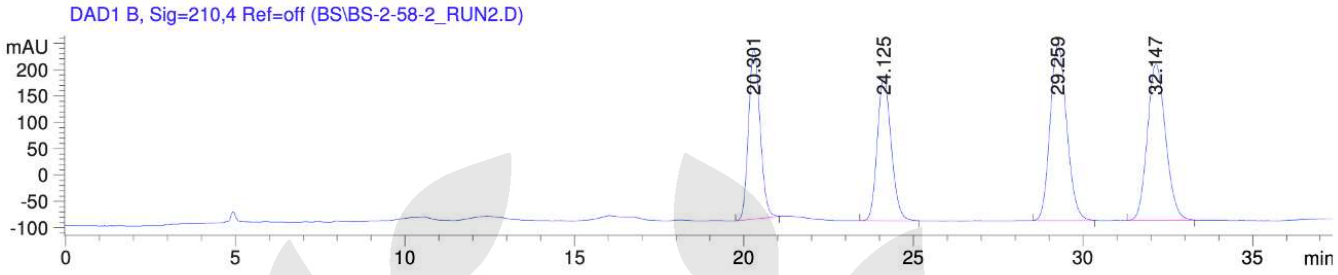




Signal 1: DAD1 A, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 10.437 | BB | 0.2273 | 98.26952 | 6.61412 | 2.4349 |
| 2 | 11.616 | BB | 0.2845 | 3194.82837 | 172.15773 | 79.1603 |
| 3 | 13.096 | BB | 0.3098 | 742.80127 | 36.43693 | 18.4049 |
| Totals : | | | | 4035.89916 | 215.20878 | |

HPLC trace of racemic **4n**



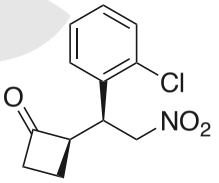



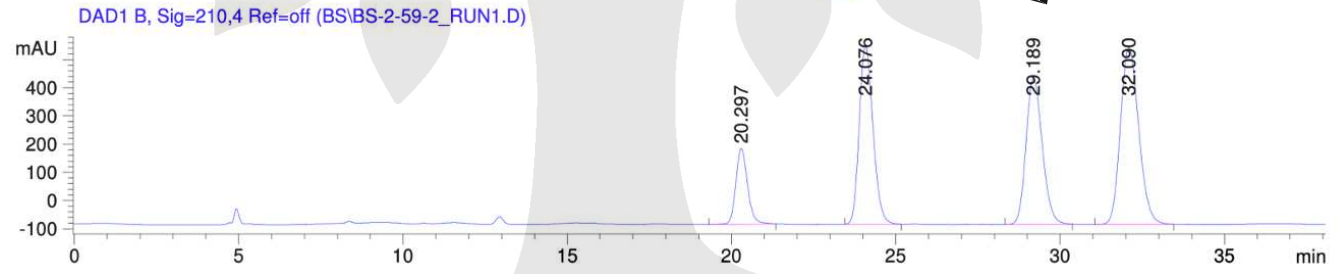

Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 20.301 | BB | 0.3712 | 7663.61523 | 322.55090 | 20.2163 |
| 2 | 24.125 | BB | 0.4447 | 7780.64209 | 272.87363 | 20.5250 |
| 3 | 29.259 | BB | 0.5239 | 1.13738e4 | 333.51102 | 30.0036 |
| 4 | 32.147 | BB | 0.5846 | 1.10901e4 | 296.34375 | 29.2552 |
| Totals : | | | | 3.79082e4 | 1225.27930 | |

Retention time of minor *anti* isomer traces: 20.3 and 24.1 minutes.

HPLC trace of enantioenriched **4n**

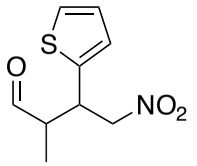


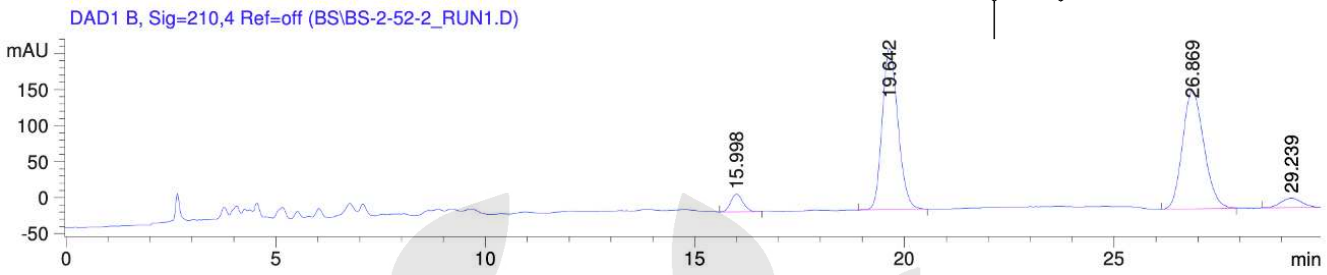




Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 20.297 | BB | 0.3798 | 6661.75781 | 268.17746 | 9.9070 |
| 2 | 24.076 | BB | 0.4557 | 1.84176e4 | 632.53235 | 27.3896 |
| 3 | 29.189 | BB | 0.5311 | 1.78715e4 | 519.81226 | 26.5774 |
| 4 | 32.090 | BB | 0.6060 | 2.42923e4 | 627.06793 | 36.1261 |
| Totals : | | | | 6.72431e4 | 2047.59000 | |

HPLC trace of racemic **4o**



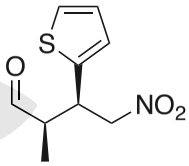



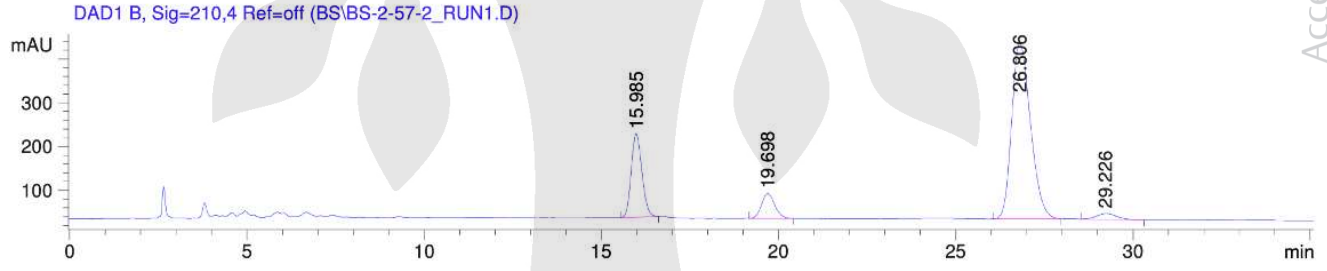

Signal 2: DAD1 B, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 15.998 | BB | 0.3157 | 502.18137 | 24.43897 | 3.9579 |
| 2 | 19.642 | BB | 0.4076 | 5889.77539 | 224.82584 | 46.4202 |
| 3 | 26.869 | BB | 0.5564 | 5831.51807 | 164.16266 | 45.9610 |
| 4 | 29.239 | BBA | 0.4235 | 464.48700 | 13.29966 | 3.6608 |
| Totals : | | | | 1.26880e4 | 426.72712 | |

Retention time of minor *anti* isomer traces: 16.0 and 29.2 minutes.

HPLC trace of enantioenriched **4o**




Signal 2: DAD1 B, Sig=210,4 Ref=off

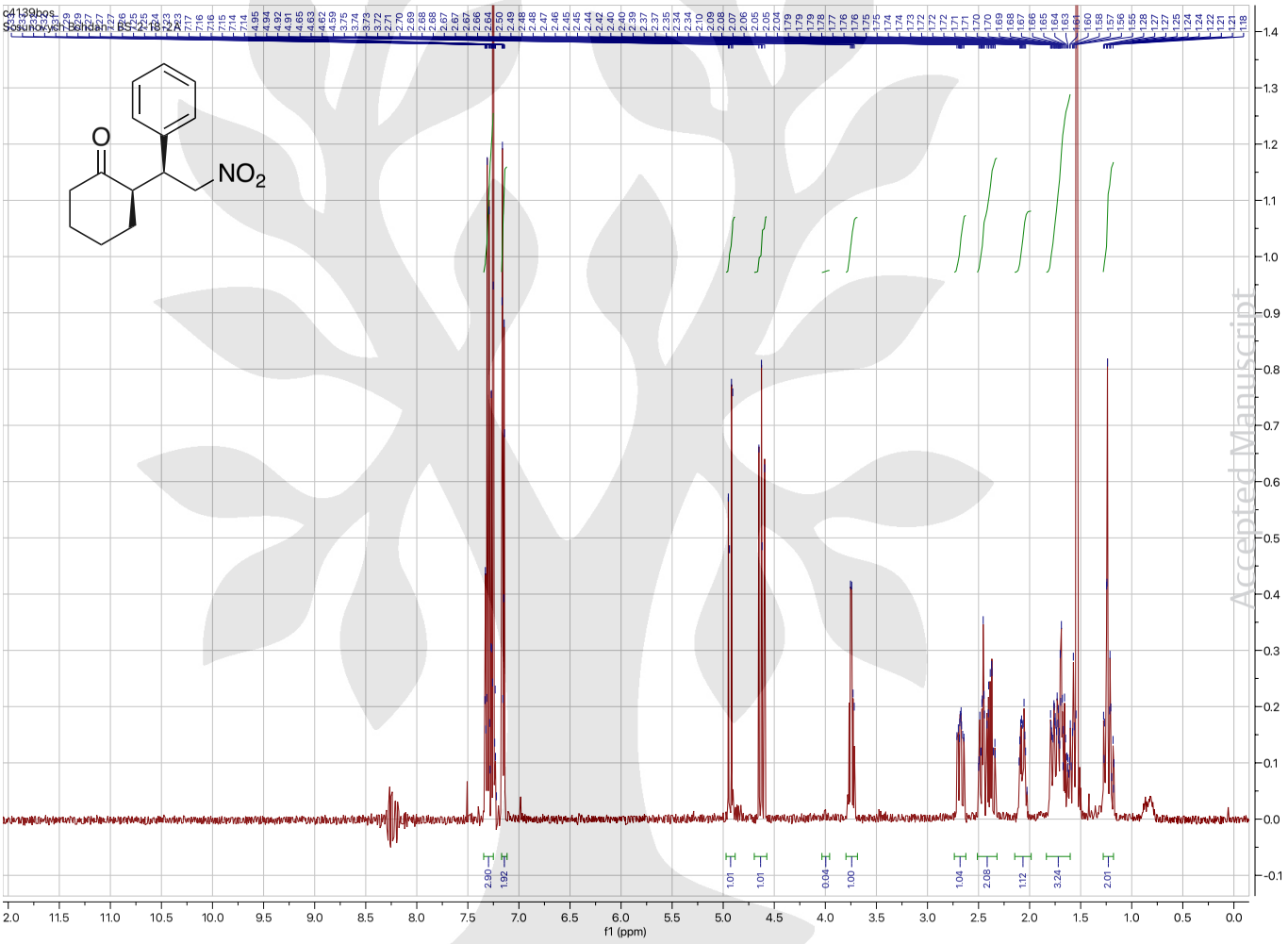
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 15.985 | BB | 0.3227 | 3997.18066 | 190.56300 | 19.2049 |
| 2 | 19.698 | BB | 0.4037 | 1484.21570 | 57.00915 | 7.1311 |
| 3 | 26.806 | BB | 0.5713 | 1.48146e4 | 402.57941 | 71.1786 |
| 4 | 29.226 | BB | 0.4689 | 517.28516 | 13.32544 | 2.4854 |
| Totals : | | | | 2.08133e4 | 663.47700 | |

## NMR Data:

After flash column chromatography

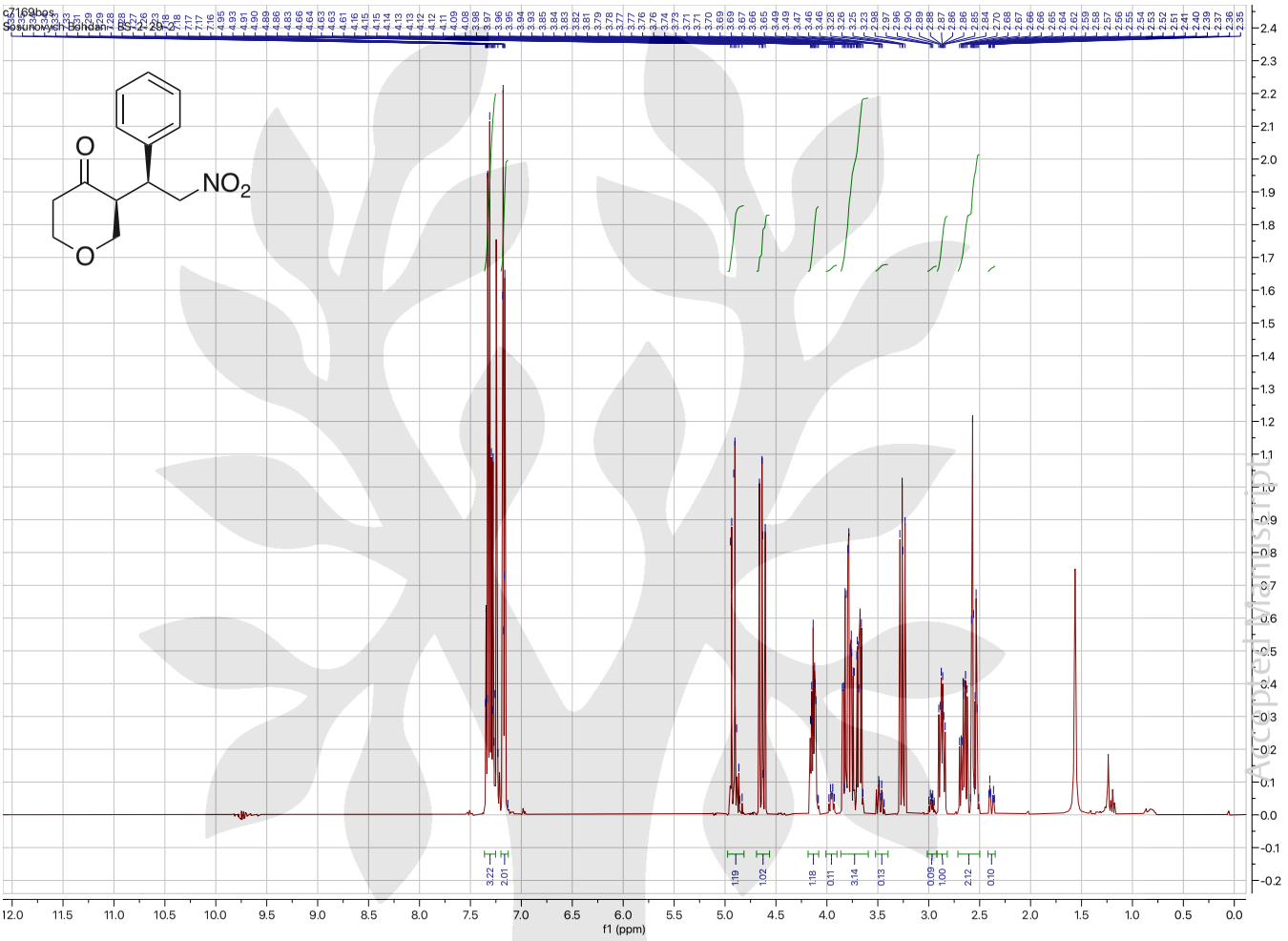
*Syn/anti* mixture **4a**. Major *syn* isomer.

| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |



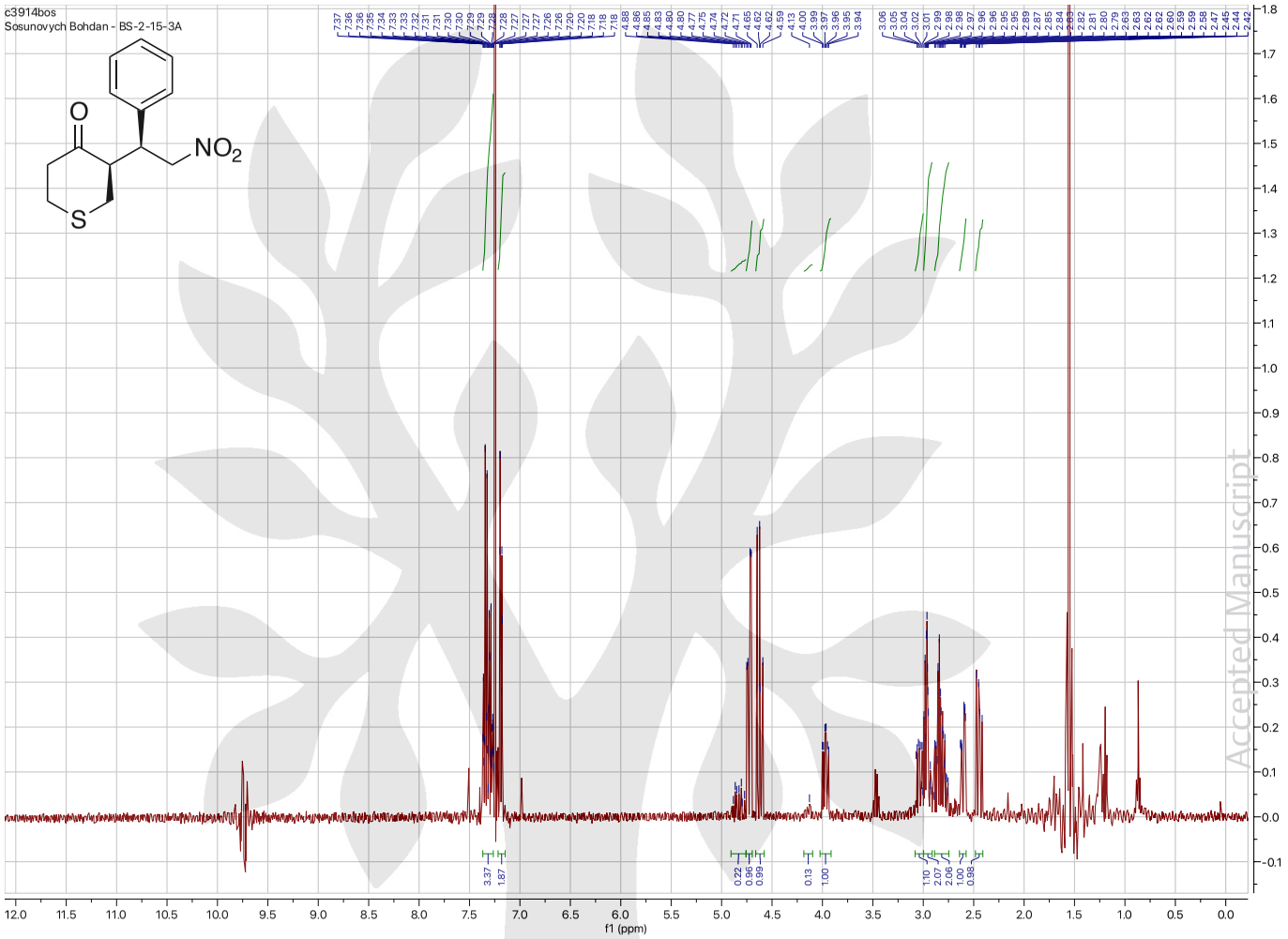
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4b**. Major *syn* isomer.



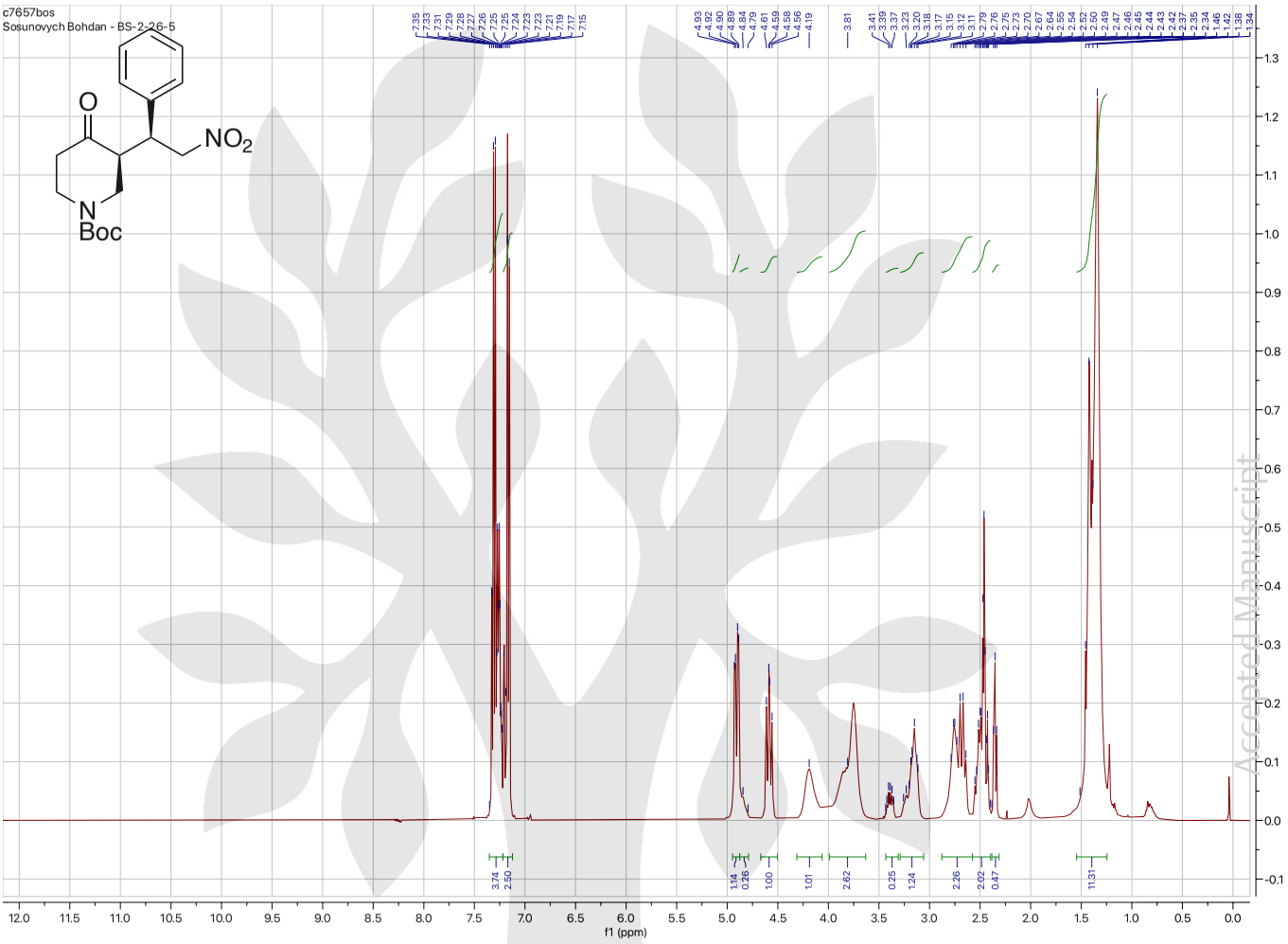
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4c**. Major *syn* isomer.



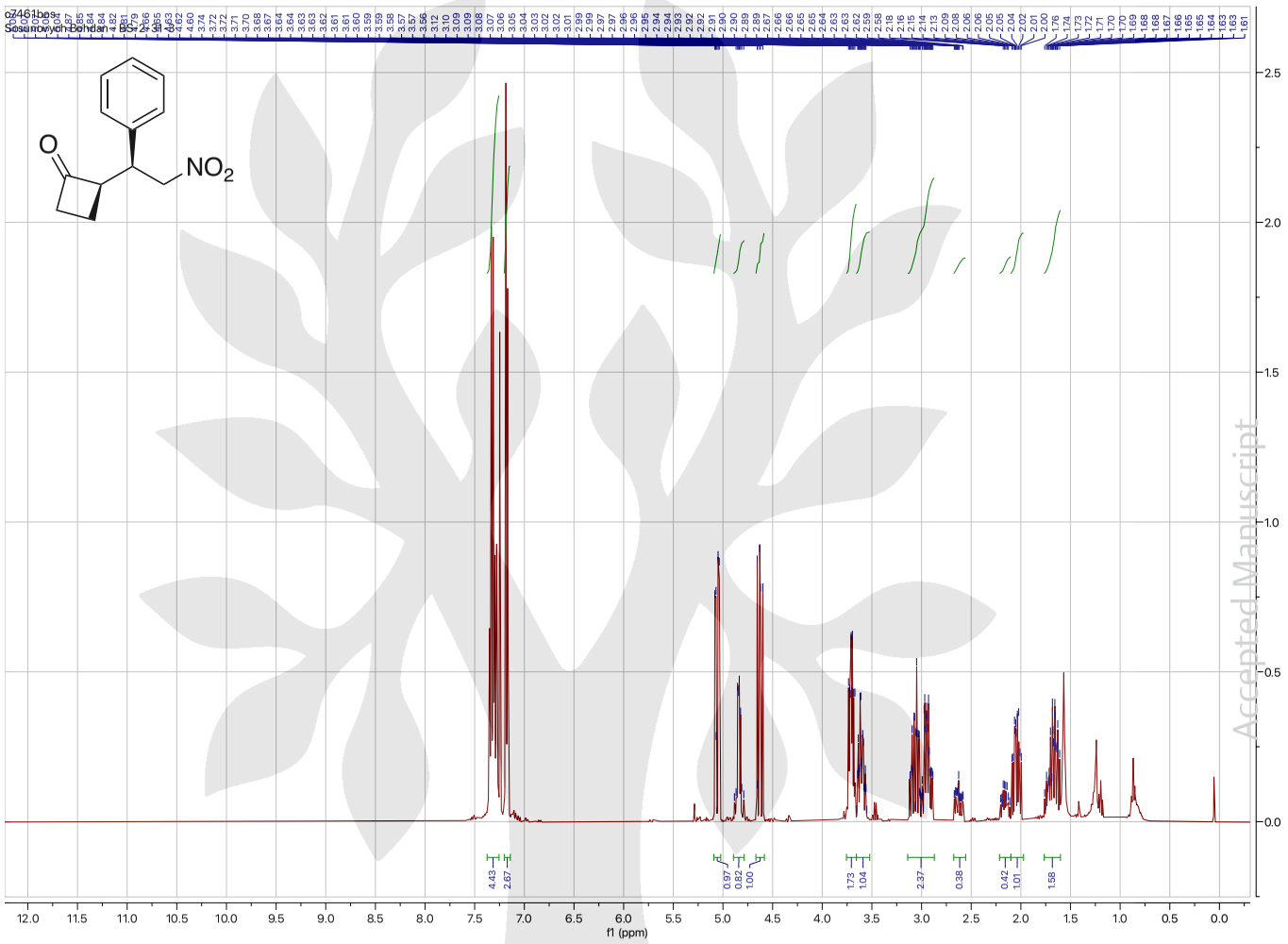
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4d**. Major *syn* isomer.



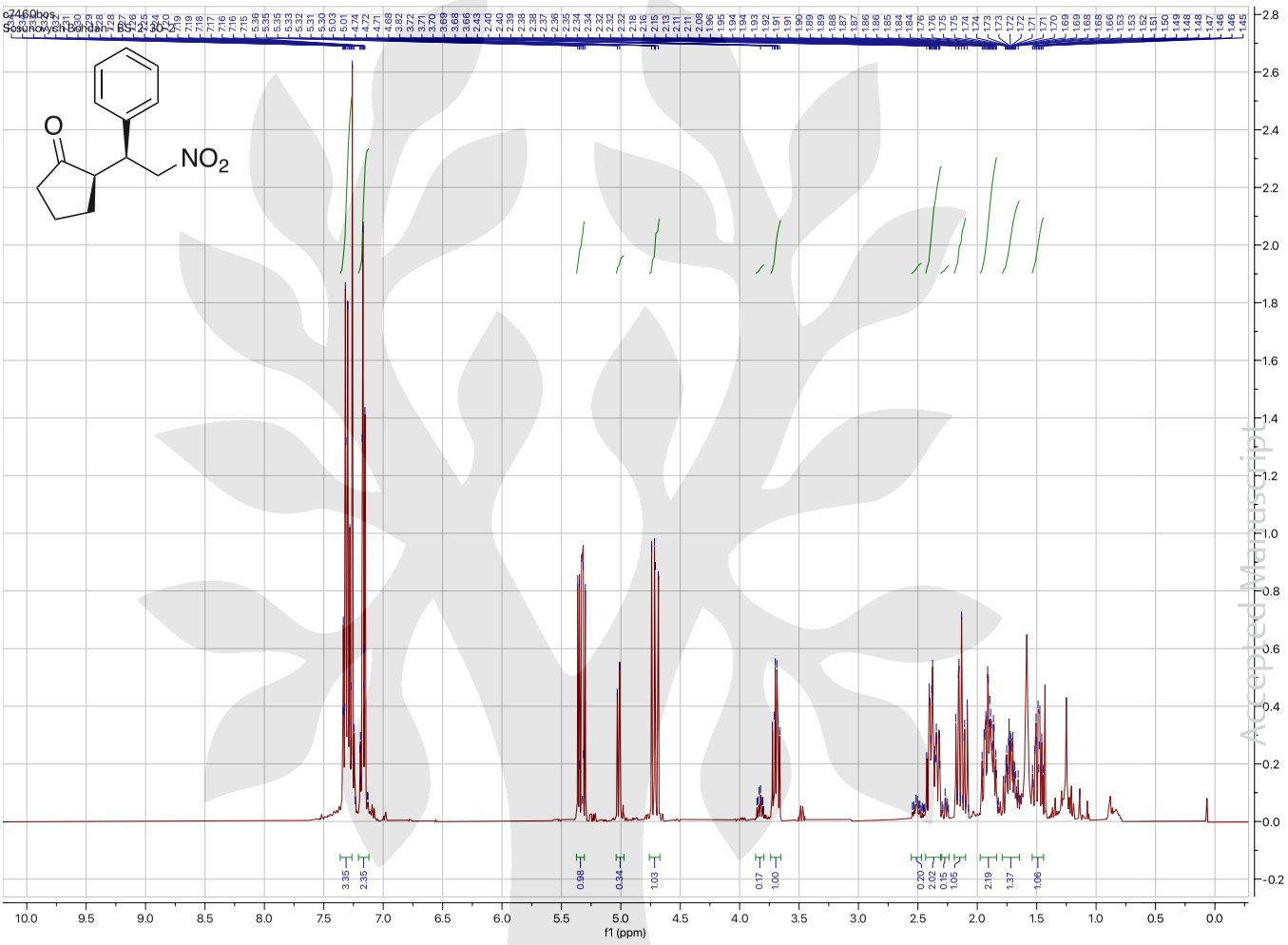
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4e**. Major *syn* isomer.



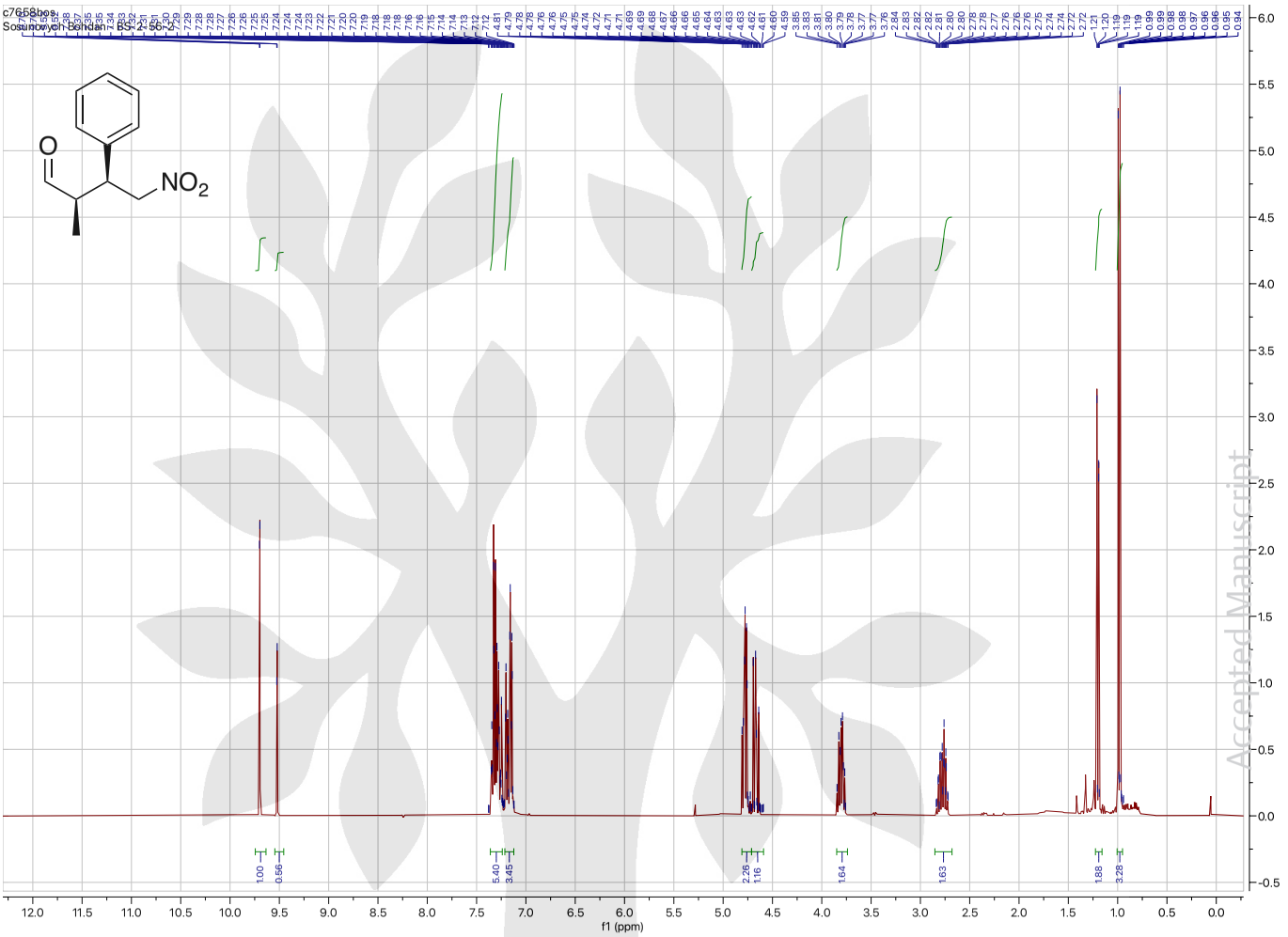
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4f**. Major *syn* isomer.



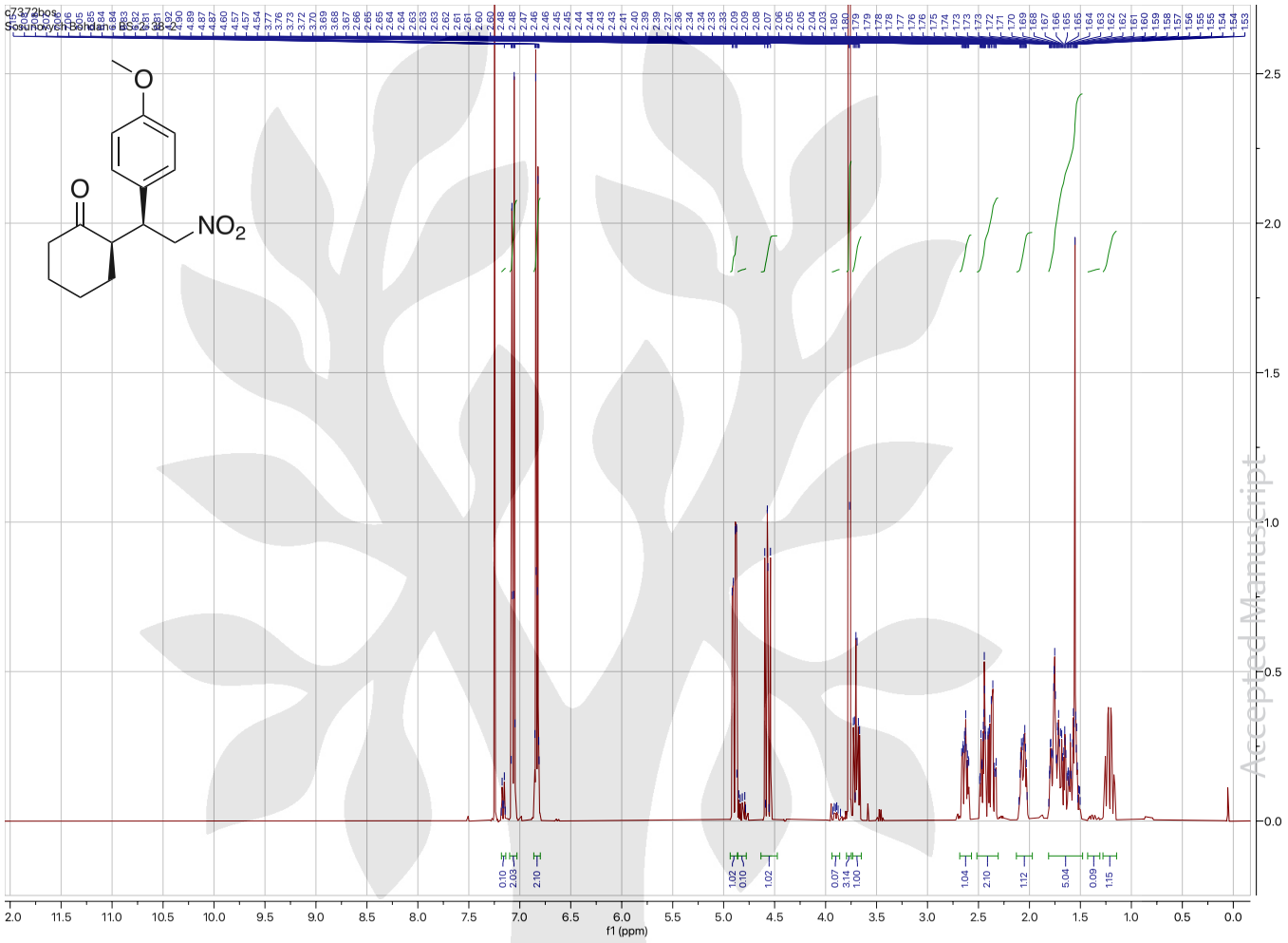
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4h**. Major *syn* isomer.



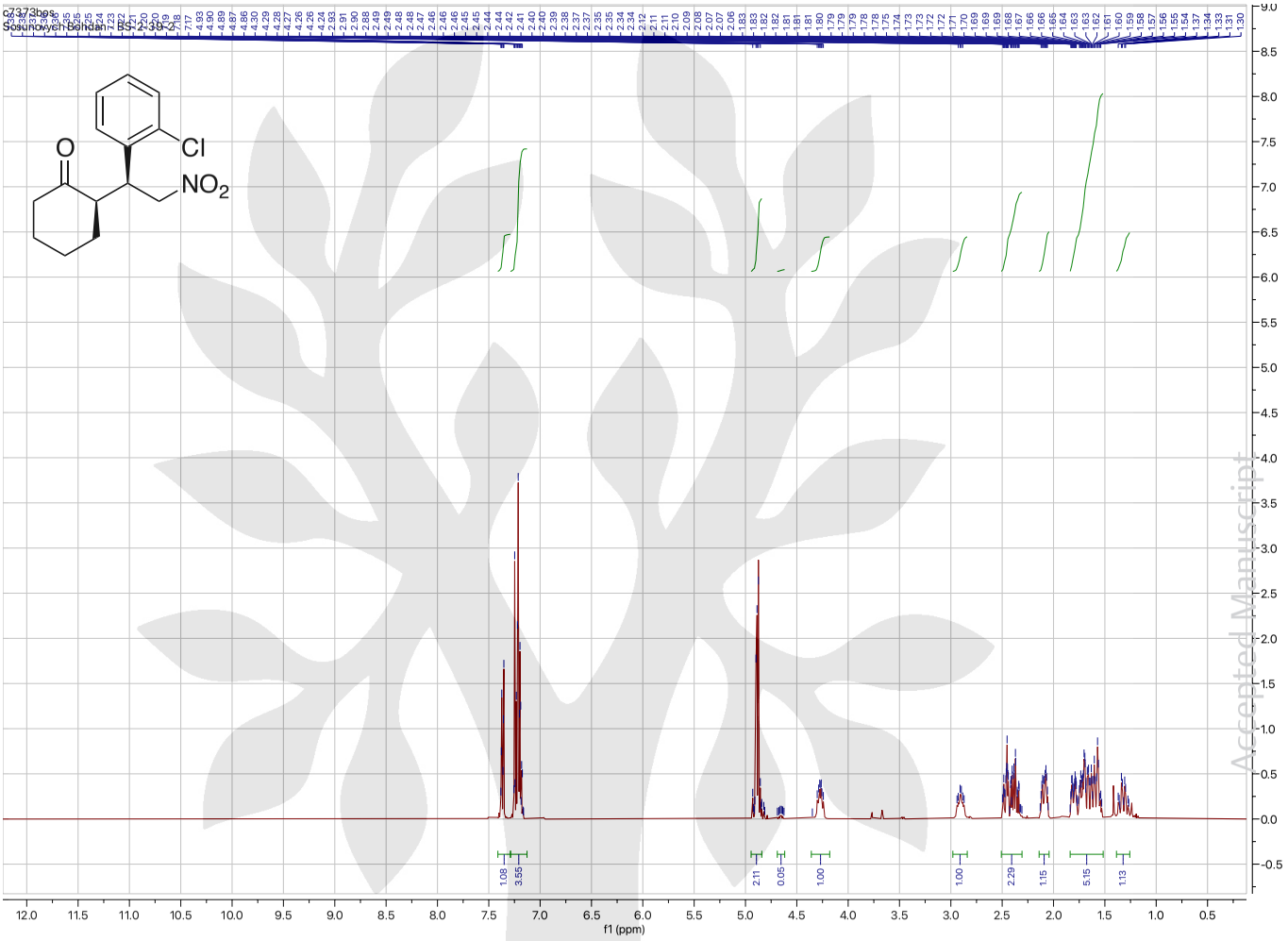
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4j**. Major *syn* isomer.



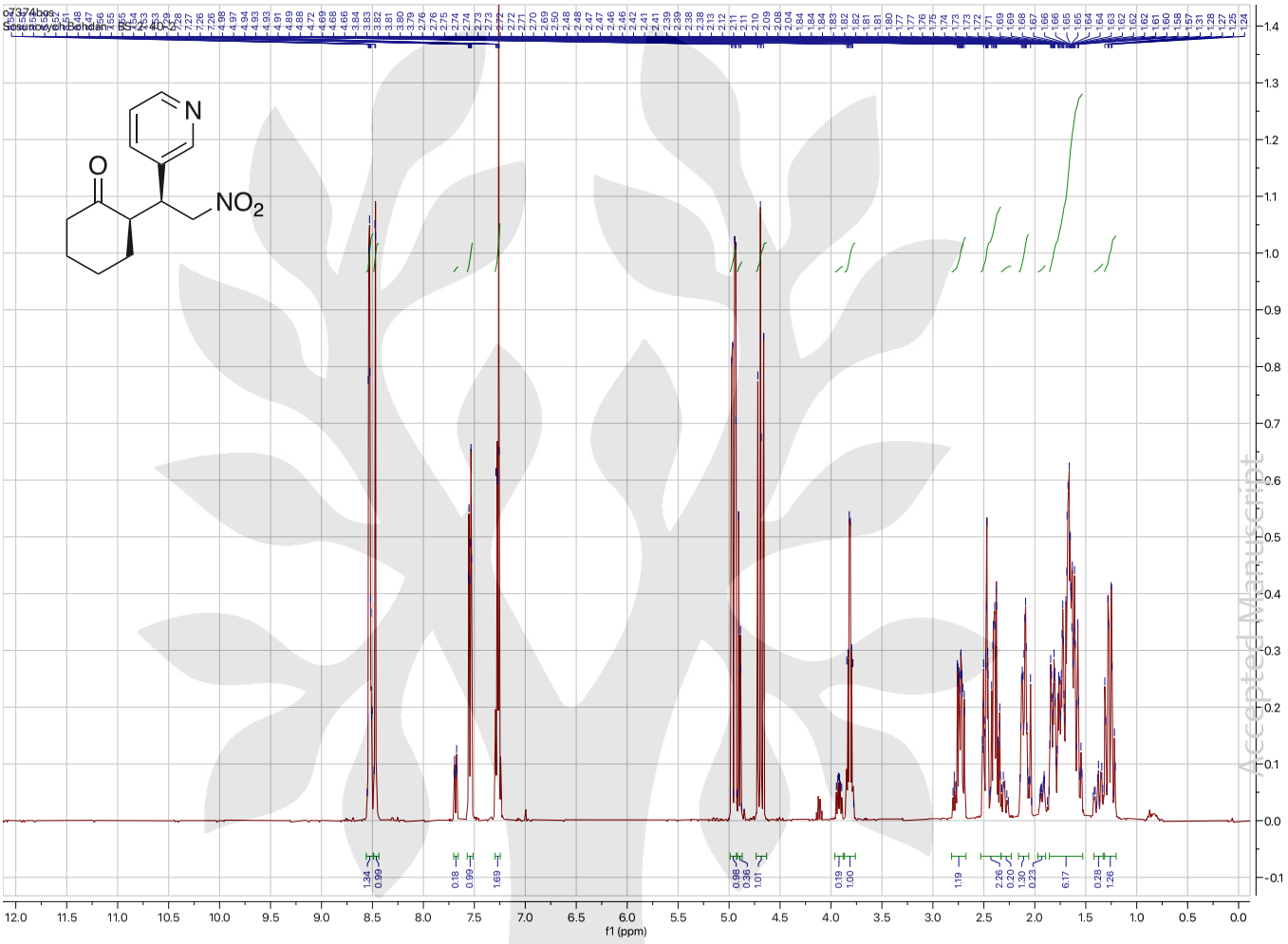
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4k**. Major *syn* isomer.



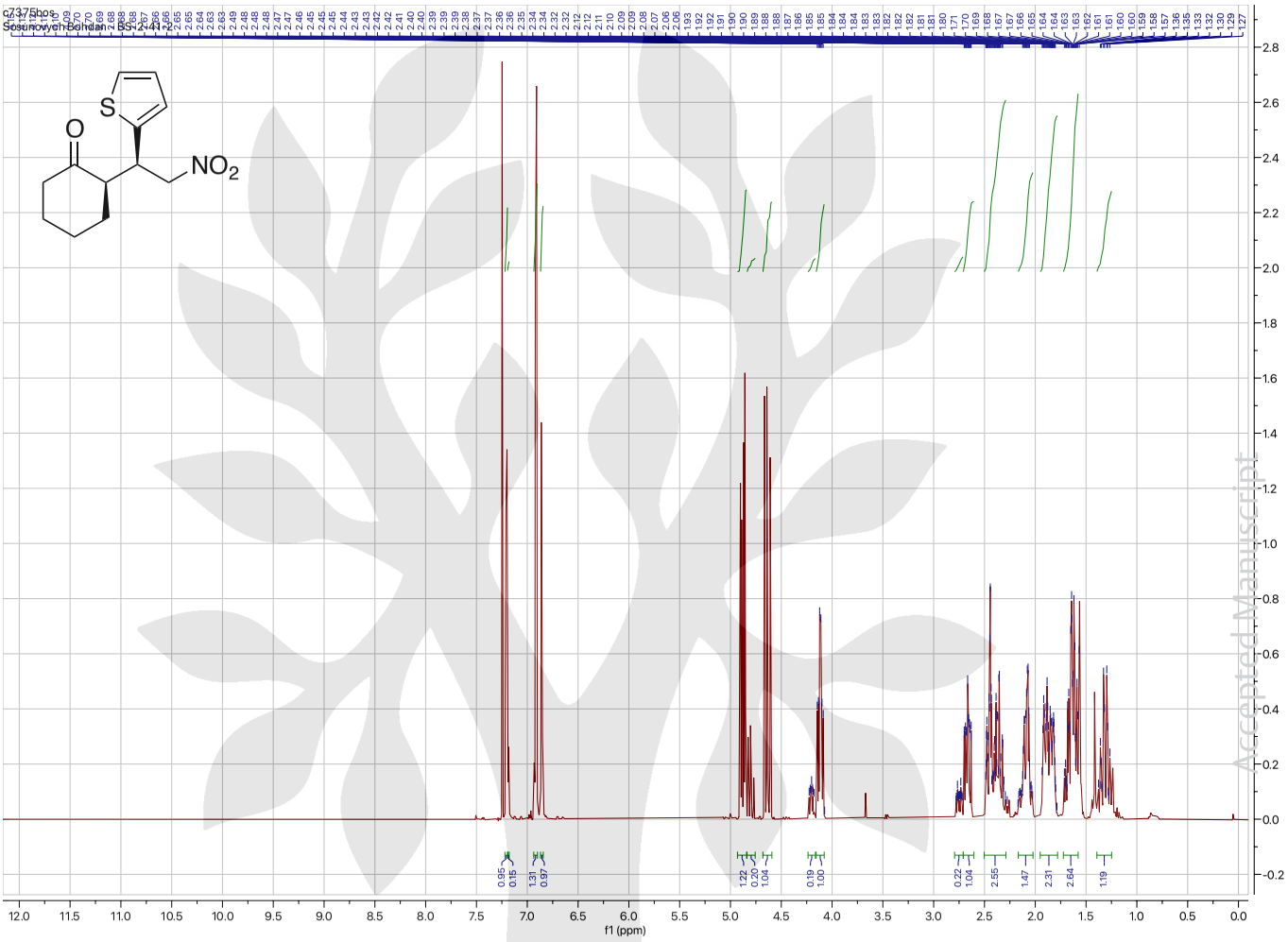
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4l**. Major *syn* isomer.



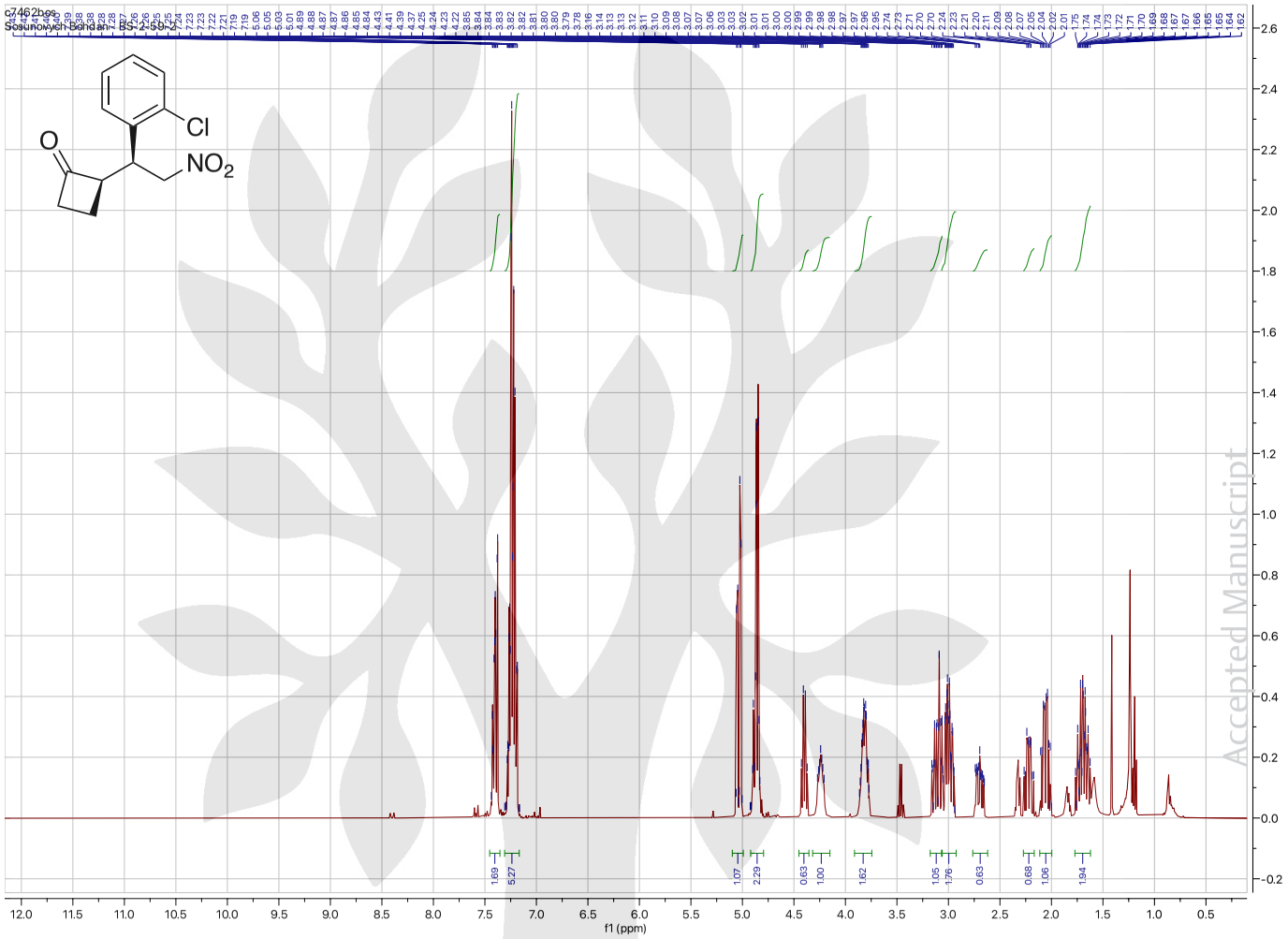
| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4m**. Major *syn* isomer.



| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4n**. Major *syn* isomer.



| Parameter | Value |
|---|---|
| Solvent | $CDCl_3$ |
| Spectrometer Frequency | 400 MHz |
| Nuclei | $^1H$ |

*Syn/anti* mixture **4o**. Major *syn* isomer.