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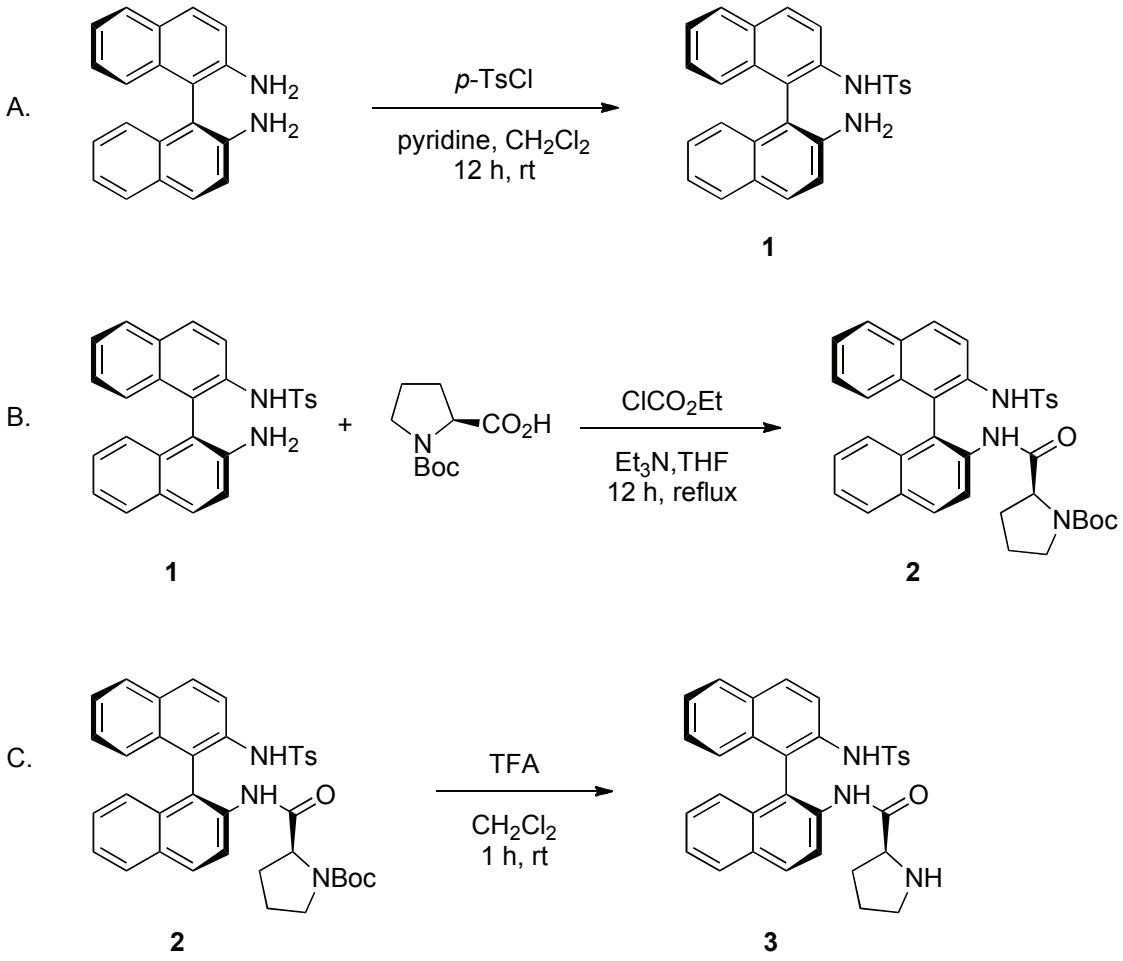
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

(S_a,*S*)-*N*-[2′-(4-METHYLPHENYLSULFONAMIDO)-1,1′-BINAPHTHYL-2-YL]PYRROLIDINE-2-CARBOXAMIDE: AN ORGANOCATALYST FOR THE DIRECT ALDOL REACTION



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Checked by David Hughes.[3]

1. Procedure

A. (S_a)-N-[2′-Amino-(1,1′-binaphthyl)-2-yl]-4-methylbenzene-sulfonamide (**1**). A 250-mL round-bottomed flask equipped with a 3-cm oval PTFE-coated magnetic stir bar is charged with (S_a)-(−)-1,1'-binaphthyl-2,2'-diamine (3.13 g, 11.0 mmol, 1.0 equiv), dichloromethane (130 mL), and pyridine (10 mL, 124 mmol, 11 equiv). To the stirred solution is added *p*-toluenesulfonyl chloride (2.03 g, 10.7 mmol, 0.97 equiv) in one portion (Note 1). The flask is sealed with a rubber septum through which is inserted

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an 18-gauge inlet needle, which is connected to a nitrogen line and a gas bubbler, and a thermocouple probe (Note 2). The brown solution is stirred at 22 °C for 10 h (Note 3). The reaction solution is concentrated by rotary evaporation (40 ºC bath temperature, 20 mmHg) to an oil that is transferred to a 500-mL separatory funnel with EtOAc (200 mL). The organic layer is washed with 2M HCl (5×30 mL) (Note 4), then vacuum-filtered through a bed of sodium sulfate (40 g) in a 150-mL medium-porosity sintered glass funnel. The filter cake is washed with EtOAc (2 x 40 mL). The filtrate is concentrated in a 500-mL round-bottomed flask by rotary evaporation (40 ºC bath, 20 mmHg), then further dried under vacuum (20 mmHg) at room temperature for 14 h to afford **1** as a pink foam (4.7 g, 82% purity, 80% yield) which is used directly in the next step (Notes 5 and 6).

B. (S_a,S)-t-Butyl 2-[(2′-(4-methylphenylsulfonamido)-(1,1′-binaphthyl)-2-yl-carbamoyl]pyrrolidine-1-carboxylate (**2**). A 250-mL round-bottomed flask equipped with a 3-cm PTFE-coated magnetic stir bar is charged with (*S*)-*N*-(*t*-butoxycarbonyl)-*L*-proline (3.00 g, 13.9 mmol, 1.6 equiv), anhydrous THF (100 mL), and triethylamine (1.42 g, 14.0 mmol, 1.6 equiv) (Note 7). The flask is sealed with a rubber septum through which is inserted an 18-gauge inlet needle, which is connected to a nitrogen line and a gas bubbler, and a thermocouple probe (Note 2). The mixture is cooled to 3 ºC with an ice-water bath and ethyl chloroformate (1.43 g, 13.2 mmol, 1.5 equiv) is added dropwise via a 3-mL syringe over 3 min where upon a fine white precipitate is formed (Note 8). The suspension is stirred 30 min at 0-5 ºC and then a solution of **1** (4.7 g, 82 wt%, 3.85 assay g, 88 mmol, 1.0 equiv) in anhydrous THF (25 mL) is added dropwise over 5 min via a 40-mL syringe. After the addition, the rubber septum is replaced with a condenser fitted with a gas adapter connected to a nitrogen line and gas bubbler. The mixture is refluxed using a heating mantle for 12 h (Note 9). At the end of the reaction, the suspension is cooled to room temperature, filtered through a 60-mL medium-porosity sintered glass funnel, and the filter cake is washed with THF (2×25 mL). The combined filtrates are concentrated by rotary evaporation (40 ºC bath temperature, 20 mmHg) in a 500-mL round bottomed flask and further dried under vacuum (20 mmHg) for 3 h to provide **2** (7.7 g, estimated 65% purity, 5.0 assay g, 90% yield) as a pink foam which is used directly in the next step (Notes 10-12).

C. (S_a,S)-N-[2′-(4-Methylphenylsulfonamido)-1,1′-binaphthyl-2-yl-pyrrolidine-2-carboxamide (**3**). The 500-mL flask containing crude **2** (7.7 g, 65% purity, 7.9 mmol) from the previous step is equipped with a 3-cm oval

PTFE-coated magnetic stir bar and charged with dichloromethane (80 mL) (Note 13). The flask is sealed with a rubber septum through which is inserted an 18-gauge inlet needle, which is connected to a nitrogen line and a gas bubbler, and a thermocouple probe (Note 2). Trifluoroacetic acid (16 mL, 208 mmol, 26 equiv) is added dropwise via a 20-mL syringe over 3 min, and the mixture is stirred at 20-22 ºC for 1 h (Notes 14 and 15). At the end of reaction, the solution is cooled to 3 ºC using an ice-water bath and the septum is removed and replaced with a 125-mL addition funnel to which is added 2.5 M sodium hydroxide (80 mL). The NaOH solution is added dropwise to the reaction mixture over 10 min (Notes 16 and 17). The mixture is transferred to a 250-mL separatory funnel, and the bottom organic layer is separated. The aq. layer is back extracted with dichloromethane (40 mL). The organic layers are combined and dried with sodium sulfate (100 g) (Note 18), then vacuum filtered through a 150-mL medium porosity sintered glass funnel into a 500-mL round bottomed flask. The filter cake is washed with dichloromethane (2x60 mL). The combined filtrate is concentrated by rotary evaporation (40 ºC bath, 20 mmHg) to ~80 mL, then silica gel (30 g) is added, and the mixture is evaporated to a free-flowing powder. The material is purified by column chromatography (Note 19) with a final concentration in a 250-mL round bottom flask. The material is dried under vacuum (room temperature, 20 mmHg, 14 h) to provide **3** as a white solid (3.9–4.1 g). A 3-cm oval PTFE-coated stir bar and dichloromethane (8 mL) are added to the flask and the contents are warmed in a 40 ºC water bath to dissolve the product, and then the flask is cooled to room temperature and is equipped with a 60-mL addition funnel. The mixture is stirred as hexanes (40 mL) are added through the addition funnel over 30 min. Crystallization occurs after 10 mL of hexanes is added, and the mixture becomes a thick slurry as the remainder of the hexanes is added. The slurry is stirred 12 h at ambient temperature and then is vacuum-filtered into a 60-mL sintered glass funnel. The filter cake is washed with 5:1 hexanes: dichloromethane (15 mL) and then is air-dried to constant weight to afford (S_a,*S*)-*N*-[2′-(4-methylphenylsulfonamido)-1,1′-binaphthyl-2-yl-pyrrolidine-2-carboxamide (**3**) as a white crystalline solid (3.8–4.0 g, step yield 89–94%, 3-step yield 65–68%) (Notes 20-22).

2. Notes

1. The following reagents and solvents in Step A were used as received: (S_a)-(–)-1,1'-binaphthyl-2,2'-diamine (Sigma-Aldrich, 99%), dichloromethane (Fisher, ACS reagent, 99.5%), EtOAc (Fisher, ACS reagent, 99%), pyridine (Sigma-Aldrich, 99%), and *p*-TsCl (Acros, 99%).

2. The internal temperature was monitored using a J-Kem Gemini digital thermometer with a Teflon-coated T-Type thermocouple probe (12-inch length, 1/8 inch outer diameter, temperature range –200 to +250 °C). There was no exotherm on addition of *p*-TsCl.

3. The reaction was monitored by thin layer chromatography on silica gel (EMD, silica gel, grade 60, F_{254}) with 1:1 EtOAc:hexanes as the eluent and visualization with UV. The diamine starting material has R_f = 0.5 (blue fluorescence) and the tosyl product has R_f = 0.6. The bis-tosyl by-product co-elutes with the mono-tosylate product. The mono- and bis-tosyl products can be separated by TLC by using an eluent of 1:6 EtOAc:hexanes and 3 elutions (bis-Ts, R_f = 0.45; mono-Ts, R_f = 0.40).

4. The acid wash removes unreacted (S_a)-(–)-1,1'-binaphthyl-2,2'-diamine, which can be recovered as follows. The combined acidic washes are neutralized with 2.5N NaOH until pH 8-10 and then are extracted with dichloromethane (3 × 30 mL). The combined organic layers are washed with brine, dried over sodium sulfate and concentrated by rotary evaporation (40 ºC, 20 mmHg) to give 0.30 g (10%) of (S_a)-Binam.

5. The mono-tosylate **1** is approximately 82% pure (80% yield), containing 7 wt% EtOAc and 11 wt% of the bis-tosylate by-product as determined by ^{1}H NMR analysis of the Ts methyl groups of the mono- and bis-tosylated species:^{1}H NMR (400 MHz, $CDCl_3$); mono-tosylate **1**: δ: 2.32; bis-tosylate: δ: 2.40. This bis-tosylate by-product is difficult to separate by standard column chromatography due to overlap of the peaks using a more polar eluent and tailing of the early eluting bis-tosylate into the mono-tosylate peak using a less polar eluent. The submitters reported preparation of a purified sample by column chromatography on silica gel eluting with hexane/EtOAc, 6:1, following a literature report.[4] The checker purified a 100 mg crude sample by reverse-phase preparative HPLC using the following conditions: column, YMC-pack ODS-AQ, 5um, 150×20 mm I.D; mobile phase, linear gradient elution: 25% MeCN/75% water to 55% MeCN/45% water over 15 min; flow rate, 25mL/min; sample dissolved in MeCN at 10mg/mL; 1 mL per injection. Fractions eluting between 7-9 min

were concentrated by rotary evaporation to remove the organic phase (bath temperature 35 °C, 10 mmHg). The remaining aqueous layer was lyophilized, affording 24 mg of mono-tosylate **1**.

6. Mono-tosylate **1** has the following spectroscopic properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3 H, CH_3), 3.29 (br s, 2 H, NH_2), 6.42 (d, J = 8.4 Hz, 1 H), 6.67 (s, 1 H, NH), 6.94–7.09 (m, 5 H), 7.20–7.25 (m, 2 H), 7.37–7.43 (m, 3 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.84 (t, J = 8.7 Hz, 1 H), 7.87 (d, J = 8.0 Hz, 1 H), 7.96 (d, J = 9.0 Hz, 1 H), 8.13 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 109.9, 118.2, 119.7, 121.8, 122.7, 123.6, 125.6, 125.9, 127.35, 127.37, 127.5, 128.37, 128.39, 129.7, 129.9, 130.9, 131.5, 133.0, 133.8, 133.9, 136.5, 142.9, 143.8; LC-MS calcd for $[M + H]^+$ 439.5; found, 439.2.

7. The following reagents and solvents in Step B were purchased from Sigma-Aldrich and used as received: *N*-(*t*-butoxycarbonyl)-*L*-proline (>99%), triethylamine (99.5%), THF (ACS reagent, >99%, inhibited with 250 ppm BHT), and ethyl chloroformate (97%).

8. Addition of ethyl chloroformate results in a slight exotherm from 3 ºC to 5 ºC.

9. The progress of the reaction can be monitored by TLC (EMD, silica gel, grade 60, F_{254}) with 1:1 EtOAc:hexanes and visualization with UV (starting material **1** has R_f = 0.45 and the Boc-proline product **2** has R_f = 0.3); however, the end of reaction cannot be determined by TLC since the unreactive bis-tosylate carried forward from step A co-elutes with the mono-tosylate. NMR of the crude reaction mixture is uninformative due to broad peaks caused by Boc rotamers. Therefore, the end of reaction was assessed by deprotecting the Boc group and determining the amount of mono-tosylate that remained unreacted by ^{1}H NMR. A ~20 mg aliquot of the reaction mixture was evaporated then dissolved in 0.5 mL of $CDCl_3$ followed by addition of 0.2 mL of TFA. The sample was reacted for 15 min at room temperature then analyzed by ^{1}H NMR. The Ts-methyl group was diagnostic for assessing reaction completion: bis-tosylate, δ 2.42; product **3**, δ 2.45; mono-Ts **1**, δ 2.52.

10. Given the broad peaks in the ^{1}H NMR spectrum (Note 12) the purity of the crude material from step B could not be estimated by NMR. The rough purity and yield estimates are based on the 65% recovery of material when subjected to flash chromatography in a separate experiment (Note 11).

11. Compound **2** (2.33 g crude weight) can be purified by column chromatography using 85 g silica gel (Fisher, 230-400 mesh, 60 Å) packed as a slurry with 2:1 hexanes: EtOAc, and eluted with 2:1 hexanes: EtOAc (600 mL), 1:1 hexanes:EtOAc (200 mL), and 1:2 hexanes: EtOAc (200 mL), taking 40 mL fractions. The desired product is obtained in fractions 16-23, (R_f = 0.3, 1:1 hexanes:EtOAc), which are combined and concentrated by rotary evaporation (40 °C, 20 mmHg) to give, after vacuum drying at room temperature to constant weight, 1.68 g of **2** (~90% purity, 65% recovery) as a pink foam.

12. At ambient temperature compound **2** is a mixture of 2 rotamers that cause broad peaks in the ^{1}H NMR and ^{13}C NMR spectra. The following NMR data were collected at 360 K where the rotamers had partially coalesced. ^{1}H NMR (600 MHz, 360 K, DMSO-d_6) δ: 0.76 (br s, 1 H), 1.06 (br s, 1 H), 1.32 (s, 9 H, C(CH_3)$_3$], 1.39 (br s, 1 H), 1.67-1.73 (m, 1 H), 2.38 (s, 3 H, CH_3), 2.74 (br s, 1 H), 3.08 (app q, *J* = 8.3 Hz, 1 H), 4.00 (dd, *J* = 8.9, 3.0, 1 H), 6.70 (d, *J* = 8.5 Hz, 1 H,), 6.88 (d, *J* = 8.5 Hz, 1 H), 7.13-7.16 (m, 1 H), 7.20-7.25 (m, 3 H), 7.37 (d, *J* = 9.0 Hz, 1 H), 7.43-7.46 (m, 2 H), 7.48 (d, *J* = 8.3 Hz, 2 H), 7.88 (br d, *J* = 8.6 Hz, 1 H), 7.94 (d, *J* = 8.2 Hz, 1 H), 7.96-7.99 (m, 2 H), 8.08 (d, *J* = 8.8 Hz, 1 H), 8.52 (br s, 1 H, NH), 8.78 (br s, 1 H, NH). ^{13}C NMR (150 MHz, 360K, DMSO-d_6) δ: 20.4, 22.1, 27.6, 29.4, 45.8, 60.0, 78.5, 122.4, 123.7, 124.5, 124.7, 124.8, 125.3, 125.93, 125.95, 126.3, 127.4, 127.5, 128.3, 128.7, 128.9, 130.9, 131.0, 131.9, 132.1, 133.3, 134,5, 137.7, 142.5, 153 (br), 171.2.

13. The following reagents and solvents in Step C were used as received: trifluoroacetic acid (Sigma-Aldrich, >99%), dichloromethane (Fisher, ACS reagent, 99.5%), silica gel (Fisher, 230-400 mesh, 60 Å), EtOAc (Fisher, ACS reagent, 99%), and hexanes (Fisher, ACS reagent, >98.5%).

14. During the TFA addition, the temperature decreases from 22 ºC to 19 ºC.

15. Reaction progress can be monitored by TLC using 2:1 EtOAc:hexanes as eluent and visualized by UV. An aliquot of the reaction mixture is quenched into a mixture of 0.5 mL of 2N NaOH and 0.5 mL of dichloromethane with the bottom organic layer sampled for TLC. R_f product **3**, 0.3; R_f starting material, **2**, 0.8; R_f bis-tosylate, 0.9.

16. Addition of NaOH is exothermic and should be added at a rate to keep the internal temperature below 35 ºC to prevent boiling of dichloromethane.

17. At the end of the NaOH addition, the pH is checked by pH paper and should be 8-10. If below 8, additional NaOH is added.

18. The organic layer is hazy due to the retention of a second phase water that is not completely removed upon drying with sodium sulfate.

19. A 6-cm diameter glass column is slurry-packed (2:1 EtOAc:hexanes) with silica gel (200 g). Crude product **3** co-mixed with silica is slurried in 2:1 EtOAc:hexanes and added to the top of the column. The column is topped with 0.5 cm of sand, then eluted with 2:1 EtOAc:hexanes (500 mL), 3:1 EtOAc:hexanes (500 mL), and EtOAc (1 L), taking 100 mL fractions. The chromatography is monitored by TLC (EtOAc, R_f 0.5). The product elutes in fractions 9-15, which are combined and concentrated by rotary evaporation (40 °C water bath, 20 mmHg) in a 1-L flask, then transferred to a 250-mL round-bottomed flask for the final concentration. The white solid is dried under vacuum (20 mmHg) at room temperature for 28 h to constant weight (3.9 – 4.1 g).

20. (S_a,*S*)-*N*-[2′-(4-Methylphenylsulfonamido)-1,1′-binaphthyl-2-yl-pyrrolidine-2-carboxamide (**3**) exhibits the following physical and spectroscopic properties: R_f 0.5 (EtOAc); $[\alpha]_D^{25}$ –95 (*c* 1.0, $CHCl_3$); mp 196-197 ºC, Lit[7d] 191-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.64–0.73 (m, 1 H), 1.15–1.28 (m, 2 H), 1.57–1.64 (m, 1 H), 1.74–1.84 (m, 1 H), 2.20–2.26 (m, 1 H), 2.35 (s, 3 H), 3.32 (dd, *J* = 4.0, 9.5 Hz, 1 H), 6.35 (br s, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 7.12 (d, *J* = 8.1, 2 H), 7.16–7.22 (m, 2 H), 7.37–7.46 (m, 4 H), 7.87 (d, *J* = 7.9 Hz, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 8.00 (d, *J* = 9.1 Hz, 1 H), 8.06 (d, *J* = 9.0, 1 H), 8.19 (d, *J* = 9.0 Hz, 1 H), 8.82 (d, *J* = 9.0 Hz, 1 H), 9.31 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 25.4, 30.7, 46.3, 60.7, 117.0, 119.4, 119.6, 120.8, 124.3, 125.3, 125.4, 125.8, 127.6, 127.8, 128.3, 128.8, 129.7, 130.3, 130.7, 130.9, 131.4, 132.3, 132.7, 133.9, 135.9. 136.7, 144.1, 173.5; Anal. calcd. for $C_{32}H_{29}N_3O_3S$: C, 71.75; H, 5.46; N, 7.84; Found: C, 71.41; H, 5.15; N, 7.73.

21. The checkers determined the enantiomeric purity by SFC using a Lux-4 column (150 x 4.6mm, 5um particle size); isocratic elution, 40% MeOH with 25 mM *i*-butylamine/60% CO_2; 3.0 mL/min flow; detection at 210 nm; 200 bar pressure; t_r (*S,S*)= 4.5 min; t_r (*R,R*)= 5.5 min; none of the enantiomer was detectable (ee >99%). The submitters determined enantiomeric purity by HPLC analysis at 254 nm using a Chiralpak AD-H column; isocratic elution, 80:20 hexanes: *i*-PrOH; 1mL/min: t_r (*R,R*)= 51 min, t_r (*S,S*)= 105 min. The (*R,R*)-enantiomer was prepared by the same procedure using (R_a)-(–)-1,1'-binaphthyl-2,2'-diamine and Boc-*D*-proline

and exhibited the following physical properties: mp 195–197 ºC; $[\alpha]_D^{25}$ +93 (*c* 1.0, $CHCl_3$).

22. The diastereomeric purity (de) was determined to be >99% by ^1H NMR analysis in comparison to the (S_a,*R*)-diastereomer, which was prepared via the same procedure except that Boc-*D*-proline was used instead of Boc-*L*-proline. One aromatic proton in the (S_a,*R*)-diastereomer is upfield (6.54 ppm doublet) relative to the (S_a,*S*)-diastereomer (6.86 ppm doublet). The 6.54 ppm doublet was undetectible (<0.5%) in the (S_a,*S*)-diastereomer. The diastereomer (S_a,*R*)-*N*-[2′-(4-methylphenylsulfonamido)-1,1′-binaphthyl-2-yl-pyrrolidine-2-carboxamide exhibits the following physical and spectroscopic properties: mp 134–137 ºC, Lit[7d] 152-155 °C; $[\alpha]_D^{25}$ + 6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.50–1.55 (m, 2 H), 1.86–2.00 (m, 2 H), 2.30–2.34 (m, 1 H), 2.34 (s, 3 H), 2.57–2.62 (m, 1 H), 3.51 (dd, *J* = 4.5, 9.5 Hz, 1 H), 6.54 (d, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 6.98 (dt, *J* = 1.1, 7.7 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 7.20–7.23 (m, 1 H), 7.34–7.41 (m, 4 H), 7.89 (dd, *J* = 8.3, 11.0 Hz, 2 H), 7.99 (d, *J* = 9.0 Hz, 1 H), 8.06 (d, *J* = 9.0 Hz, 1 H), 8.15 (d, *J* = 9.0 Hz, 1 H), 8.80 (d, *J* = 9.0 Hz, 1 H), 9.65 (br s, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 26.1, 30.9, 47.0, 61.0, 117.6, 118.9, 120.0, 120.3, 124.7, 124.9, 125.6, 127.2, 127.3, 127.6, 128.3, 128.5, 129.8, 130.2, 130.7, 130.9, 131.2, 132.5, 132.9, 134.0, 135.8, 136.4, 144.0, 174.1.

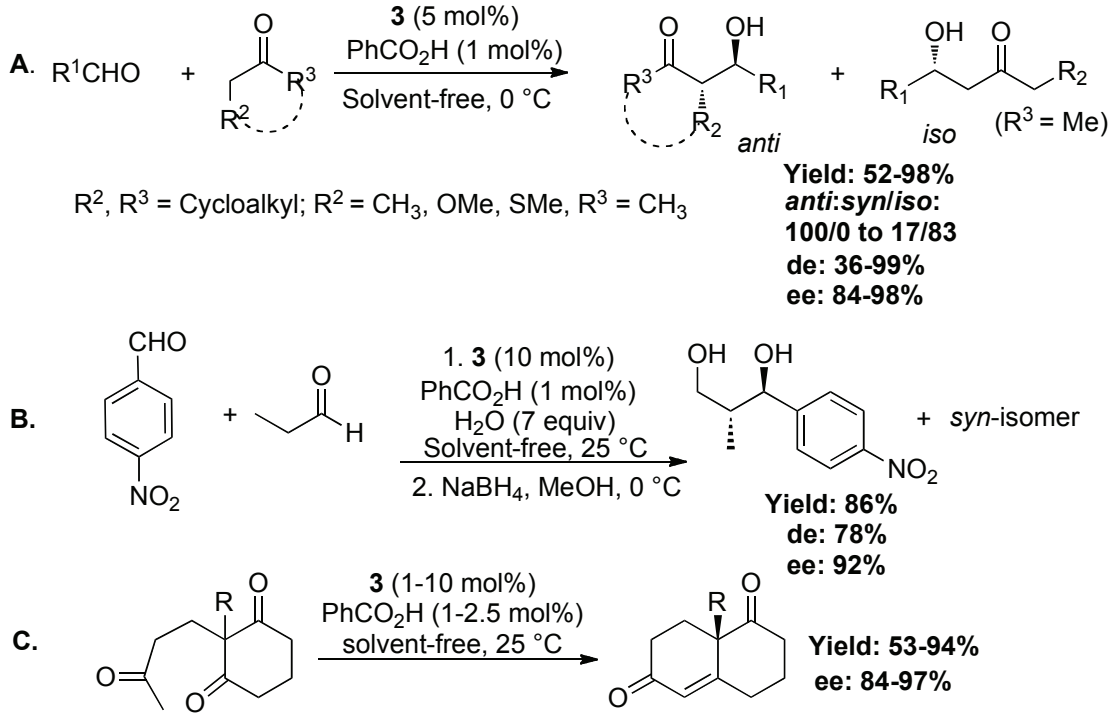
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The first generation of BINAM-prolinamides was introduced by several groups in 2006 to use in direct asymmetric aldol reactions[5-7] or other enantioselective processes.[8] (S_a,*S*)-*N*-[2-(4-Methylphenylsulfonamido)-1,1′-binaphthyl-2′-yl]-pyrrolidine-2-carboxamide (**3**) is a novel BINAM-prolinamide-type organocatalyst[5] that was developed by Nájera´s group[9] and others[7d] almost simultaneously. This (S_a)-binam-*L*-prolinamide sulfonamide derivative **3**[9] was designed by replacing one proline residue in the first generation catalyst[7] with an acidic sulfonamide group that could activate the

carbonyl group of the acceptor through hydrogen-bonding.[10] The efficiency of this catalyst when used with a small amount of benzoic acid as an additive has been proven in several aldol reactions, including the intermolecular aldol reaction between aldehydes and ketones (A, Scheme 1), the cross-aldol reaction between aldehydes (B, Scheme 1), and the intramolecular aldol reaction for the synthesis of the Wieland Miescher ketone (WMK) and related analogues (C, Scheme 1).



Scheme 1. Aldol processes catalyzed by *N*-tosyl-(S_a)-binam-*L*-prolinamide **3**

For all the processses, solvent-free reaction conditions could be applied using low catalyst loadings, obtaining the corresponding aldol products with good yields and diastereo- and enantioselectivities comparable to those achieved with other structurally similar catalysts[11] under different reaction conditions. For instance, the large-scale synthesis of the Wieland-Miescher ketone[12] requires only 1 mol% of catalyst **3** (see accompanying article).[13]

The preparation of catalyst **3** described here is a variant of those which already exist,[9,10] and offers the following advantages:

1) Minimal purification steps: only the final product needs to be purified by chromatography.

2) The amide bond formation is efficiently accomplished using ethyl chloroformate, which avoids the use of $SOCl_2$ to form the acid chloride or the need for expensive coupling agents that, moreover, are difficult to remove at the end of the reaction.

This preparation can be also applied to obtain the enantiomer of the desired product, (R_a,*R*)-*N*-[2′-(4-methylphenylsulfonamido)-1,1′-binaphthyl-2-yl]pyrrolidine-2-carboxamide, as well as the (R_a,*S*)- and (S_a,*R*)-diastereomers.

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Appendix
Chemical Abstracts Nomenclature (Registry Number);

(S_a)-(-)-1,1′-Binaphthyl-2,2′-diamine: (S_a)-(-)-1,1′-Bi(2-naphthylamine); (18531-95-8)

p-Toluenesulfonyl chloride: Benzenesulfonyl chloride, 4-methyl-; (98-59-9)

Pyridine; (110-86-1)

N-(*tert*-Butoxycarbonyl)-*L*-proline; (15761-39-4)

Ethyl chloroformate: Carbonochloridic acid, ethyl ester; (541-41-3)

Triethylamine; (121-44-8)

Trifluoroacetic acid; (76-05-1)

Josep Bonjoch was born in Barcelona (Catalonia, Spain) in 1952. He received his Ph.D. degree (1979) under the supervision of Prof. Joan Bosch at the University of Barcelona, Faculty of Chemistry. He then moved to the Faculty of Pharmacy at the same University, where he was promoted to Associate Professor (1984) and subsequently became Full Professor of Organic Chemistry in 1992. His main research involves the synthesis of complex nitrogen containing natural products, as a motive for developing new synthetic methodology.

Santiago Viózquez was born in Alicante (Spain) in 1981. He received his B.S. degree in chemistry at the Universidad de Alicante in 2006. He is now pursuing his Ph.D. at the Universidad de Alicante under the supervision of G. Guillena and C. Nájera. His research concerns asymmetric organocatalysis with prolinamides derivatives.

Gabriela Guillena received her BSc degree (1993) from University of Alicante. After spending one year as postgraduate student in the group of D. Seebach at the ETH (Zurich), she returned to University of Alicante and received her MSc (1995) and PhD (2000) degrees under the supervision of C. Nájera. After two years as a postdoctoral fellow at research group of G. van Koten (University of Utrecht, Netherlands), she returned to the University of Alicante where she became Assistant Professor in 2003 and Associate Professor in 2008. Her current research interests are focused on new organic methodologies and asymmetric organocatalysis.

Carmen Nájera obtained her B.Sc. (1973) from University of Saragossa and her PhD (1979) at the University of Oviedo under the supervision of J. Barluenga and M. Yus. She performed her postdoctoral work at the ETH (Zurich) with D. Seebach, at the Dyson Perrins Laboratory (Oxford) with J. E. Baldwin, at Harvard University with E. J. Corey, and at Uppsala University with J.-E. Bäckvall. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. Her scientific contributions are focused on synthetic organic chemistry such as sulfone chemistry, new peptide coupling reagents, oxime-derived palladacycles, asymmetric metal catalysis and organocatalysis.

Ben Bradshaw was born in 1974 in Southport, England. He studied Chemistry at the University of Manchester, where he obtained his PhD in 2001 under the supervision of Professor John Joule. After postdoctoral work with Professor Jim Thomas on the total synthesis of the Bryostatins he joined the group of Professor Josep Bonjoch at the University of Barcelona. In 2008 he was promoted to the position of assistant professor where his research interests include the application of organocatalysis to the total synthesis of complex natural products.

Gorka Etxebarria-Jardí was born in 1981 in Barcelona, Catalonia. He obtained his BSc in Chemistry (2004) and MSc in synthesis of antiretroviral nucleoside drugs (2005) from the University of Barcelona. In 2006, he joined the research group of Prof. Josep Bonjoch and is currently completing his Ph.D in asymmetric catalysis and natural product synthesis.

32077-142
S-Binam-tosylate
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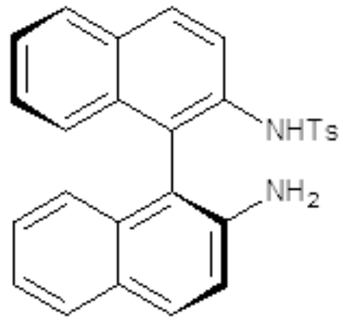

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16	7.3912	2955.5192	1.47
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19	7.2705	2907.2549	6.65
20	7.2488	2898.5777	1.52
21	7.2458	2897.3781	1.52
22	7.2398	2894.9789	1.64
23	7.2374	2894.0192	1.68
24	7.2317	2891.7399	1.51
25	7.2280	2890.2604	2.72
26	7.2238	2888.5810	3.03
27	7.2200	2887.0615	3.06
28	7.2104	2883.2227	1.68
29	7.2075	2882.0631	1.63
30	7.2023	2879.9838	1.64
31	7.2001	2879.1040	1.56
32	7.0920	2835.8781	5.23
33	7.0704	2827.2409	6.28
34	7.0525	2820.0832	2.22
35	7.0129	2804.2484	5.29
36	6.9923	2796.0111	4.78
37	6.9794	2790.8527	1.57
38	6.9764	2789.6531	1.55
39	6.9621	2783.9350	1.51
40	6.9588	2782.6154	2.59
41	6.9553	2781.2159	1.69
42	6.9411	2775.5377	1.45
43	6.9382	2774.3781	1.38
44	6.6735	2668.5325	3.40
45	6.4304	2571.3241	2.68
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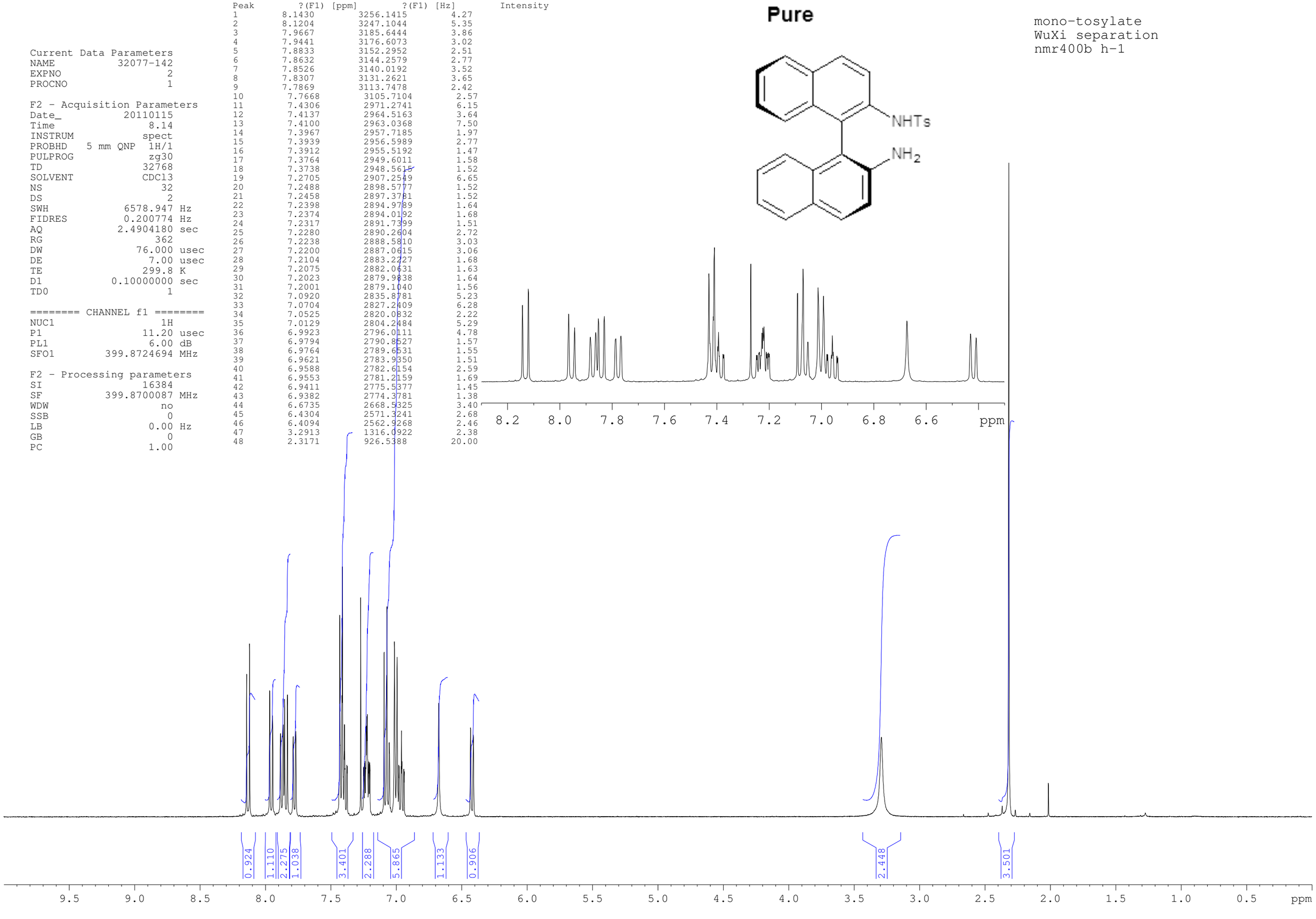

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mono-tosylate
WuXi separation
nmr400b c-13

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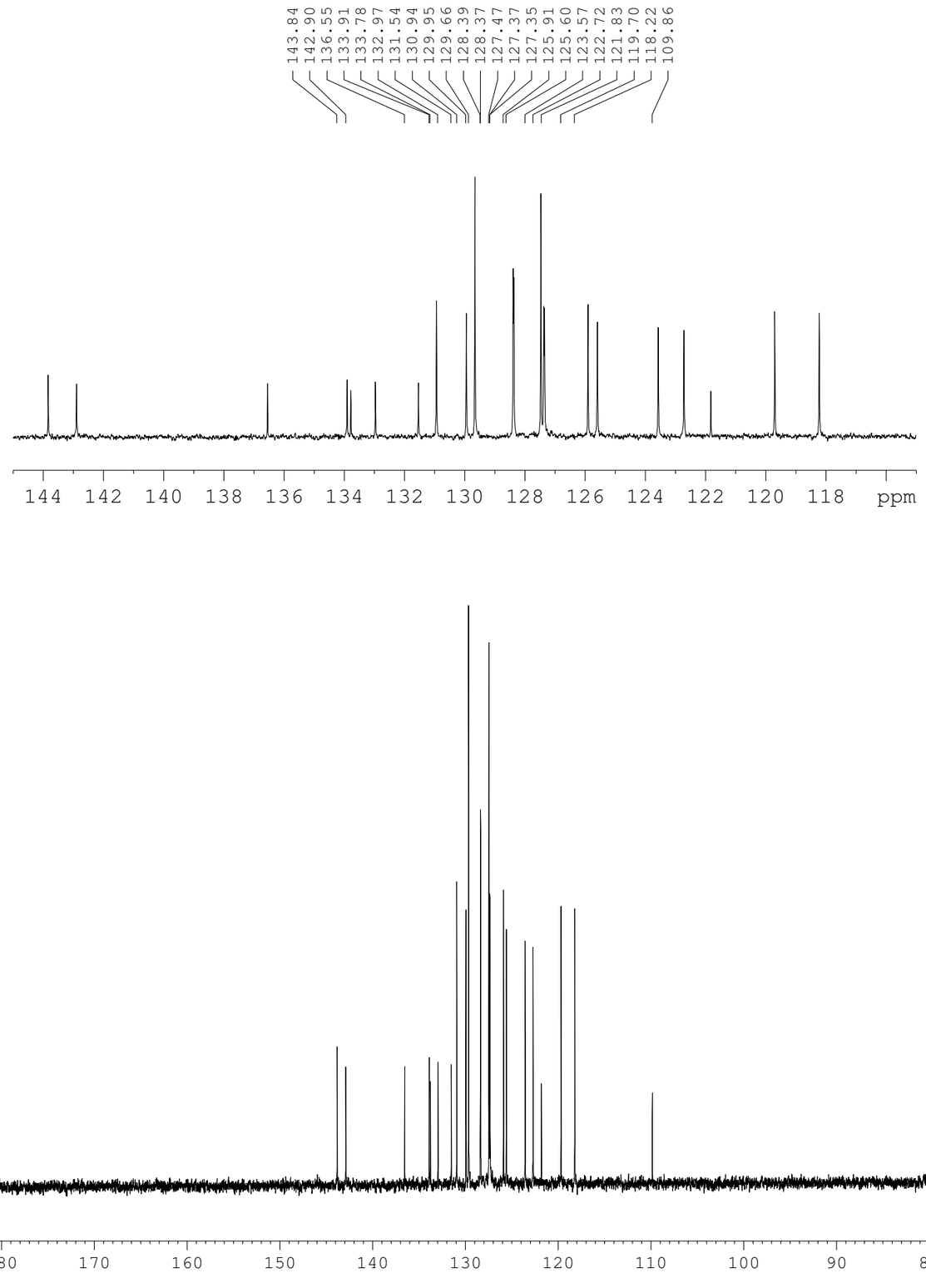

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7	131.5401	13226.0111	1.17
8	130.9423	13165.9039	2.83
9	129.9503	13066.1609	2.62
10	129.6632	13037.2938	5.43
11	128.3936	12909.6388	3.50
12	128.3718	12907.4469	3.33
13	127.4698	12816.7532	5.13
14	127.3742	12807.1408	2.76
15	127.3513	12804.8383	2.81
16	125.9097	12659.8892	2.77
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22	118.2250	11887.2128	2.64
23	109.8580	11045.9330	0.91
24	77.5539	7797.8407	14.58
25	77.4378	7786.1671	0.89
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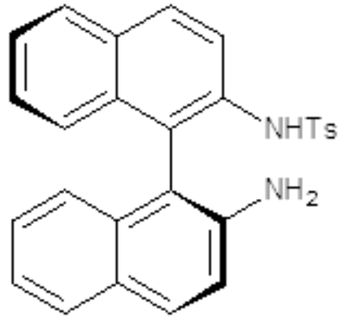
Pure



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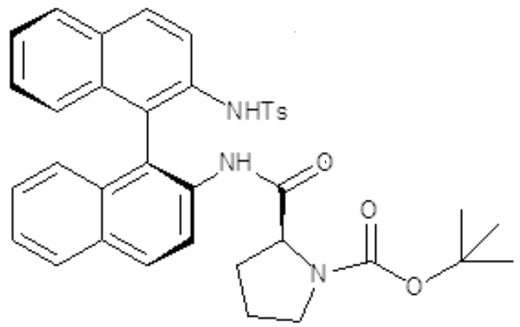

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6	3.3394		2004.0741	0.06	
7	3.0908		1854.8818	0.10	
8	3.0771		1846.6600	0.20	
9	3.0612		1837.1180	0.21	
10	3.0477		1829.0162	0.11	
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17	2.3843		1430.8900	0.06	
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21	1.8220		1093.4369	0.04	
22	1.7373		1042.6058	0.06	
23	1.7217		1033.2438	0.12	
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26	1.7048		1023.1016	0.15	
27	1.7009		1020.7611	0.14	
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29	1.6880		1013.0194	0.13	
30	1.6726		1003.7774	0.07	
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32	1.3925		835.6810	0.48	
33	1.3490		809.5754	0.05	
34	1.3426		805.7345	0.08	
35	1.3368		802.2538	0.12	
36	1.3307		798.5930	0.18	
37	1.3229		793.9120	0.19	
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39	1.2096		725.9172	0.05	
40	1.1976		718.7157	0.11	
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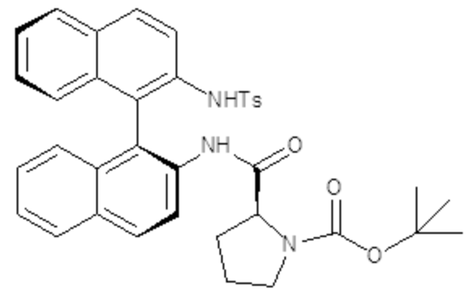

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DW                  40.400 usec
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TE                  360.0 K
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10	8.5244	5115.7482	0.39
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19	7.9649	4779.9754	0.59
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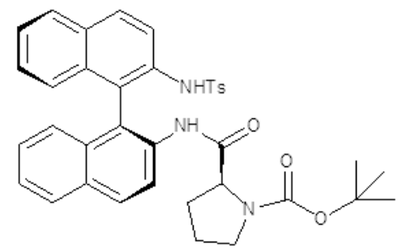
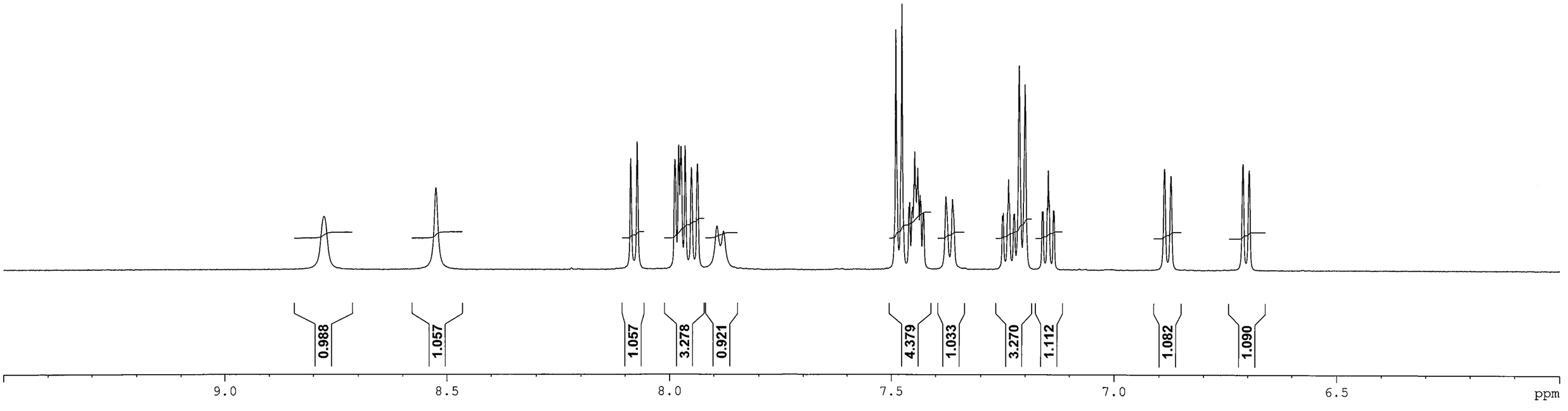
73	6.6977	4019.4907	0.48

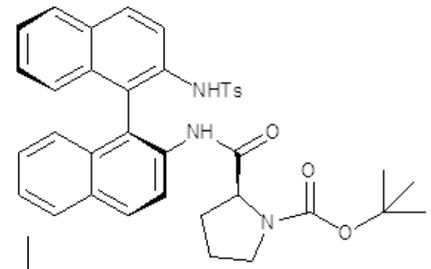




hughes 32077-137 dmso-d6
t=360k nmr600 c-13

```
Current Data Parameters
NAME      hugc0305445-0284
EXPNO                    6
PROCNO                   1

F2 - Acquisition Parameters
Date_            20101214
Time                21.28
INSTRUM             spect
PROBHD   5 mm Multinucl
PULPROG              zgdc
TD                 131072
SOLVENT             CDCl3
NS                   8192
DS                     32
SWH             40000.000 Hz
FIDRES          0.305176 Hz
AQ              1.6384625 sec
RG                   8192
DW                 12.500 usec
DE                  6.00 usec
TE                 360.0 K
D1             0.10000000 sec
d11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                   8.00 usec
PL1                 -5.00 dB
SFO1          150.9194083 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2               80.00 usec
PL2                120.00 dB
PL12                18.00 dB
SFO2          600.1330006 MHz

F2 - Processing parameters
SI                   65536
SF            150.9029515 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

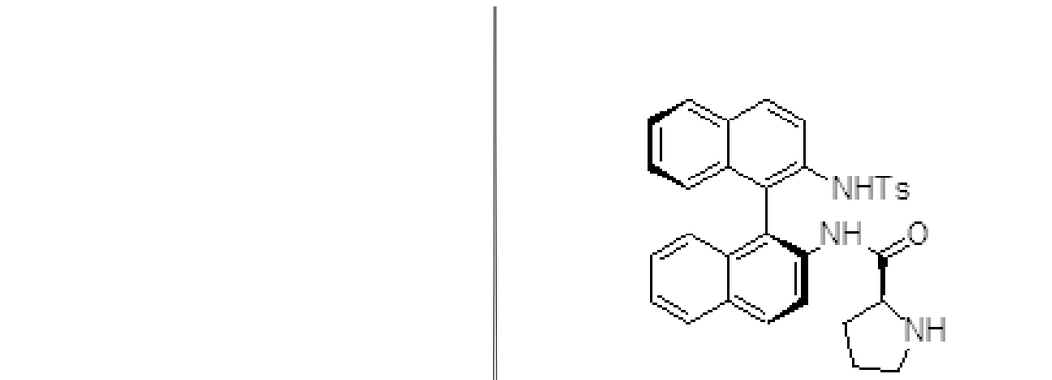
171.22
142.49 137.74 134.52 133.34 132.12 131.86 131.04 130.91 128.89 128.71 128.31 127.47 127.41 126.47 126.32 125.95 125.93 125.28 124.82 124.70 124.47 123.72 122.42 120.93 116.99 113.70 112.08 110.11 106.55 105.84 104.14
78.52
60.01
45.78 40.05 39.93 39.09
29.41 27.57 22.09 20.41



? Boc 153.

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

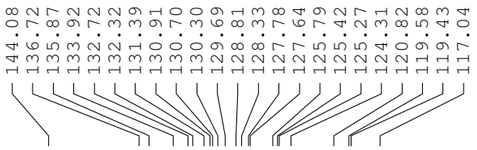
```
Current Data Parameters
NAME          32077-139
EXPNO                 5
PROCNO                1

F2 - Acquisition Parameters
Date_          20101218
Time              15.55
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                  32
DS                   2
SWH            6561.680 Hz
FIDRES         0.200247 Hz
AQ             2.4970479 sec
RG                 256
DW                76.200 usec
DE                 7.00 usec
TE                300.2 K
D1           0.10000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                1H
P1                 9.40 usec
PL1               -5.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                16384
SF          400.1300045 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

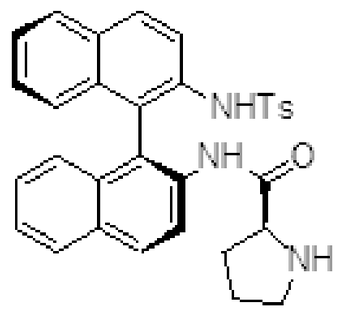


32077-139
crystallized
nmr400c h-1

Peak	?(F1) [ppm]	?(F1) [Hz]	Inter
1	9.3092	3724.8902	2.31
2	8.8353	3535.2686	3.91
3	8.8127	3526.2257	4.20
4	8.2035	3282.4665	3.68
5	8.1809	3273.4236	4.68
6	8.0788	3232.5703	3.57
7	8.0562	3223.5273	3.38
8	8.0124	3206.0016	4.01
9	7.9897	3196.9187	3.26
10	7.9600	3185.0348	2.86
11	7.9395	3176.8322	3.08
12	7.8868	3155.7453	2.84
13	7.8664	3147.5827	3.07
14	7.4534	2982.3290	7.22
15	7.4331	2974.2063	8.16
16	7.4181	2968.2044	1.90
17	7.4028	2962.0824	1.64
18	7.3837	2954.4399	2.81
19	7.3652	2947.0375	1.71
20	7.2711	2909.3853	2.94
21	7.2237	2890.4191	1.63
22	7.2018	2881.6563	3.61
23	7.1827	2874.0138	3.39
24	7.1626	2865.9712	1.62
25	7.1307	2853.2070	5.75
26	7.1104	2845.0844	5.08
27	6.9506	2781.1436	3.13
28	6.9294	2772.6609	2.71
29	6.8799	2752.8544	3.11
30	6.8589	2744.4517	2.72
31	3.3329	1333.5933	1.54
32	3.3229	1329.5920	1.70
33	3.3091	1324.0702	1.70
34	3.2991	1320.0689	1.61
35	2.3688	947.8280	20.00
36	2.2606	904.5339	0.77
37	2.2387	895.7710	1.42
38	2.2206	888.5287	1.47
39	2.2013	880.8062	0.81
40	1.8368	734.9588	0.38
41	1.8138	725.7558	0.84
42	1.8045	722.0346	0.67
43	1.7951	718.2734	0.94
44	1.7815	712.8316	1.23
45	1.7723	709.1504	0.62
46	1.7631	705.4692	1.15
47	1.7402	696.3062	0.55
48	1.6413	656.7334	0.57
49	1.6301	652.2519	1.09
50	1.6199	648.1706	0.95
51	1.6124	645.1696	1.32
52	1.5995	640.0079	1.08
53	1.5878	635.3264	0.70
54	1.5808	632.5255	0.80
55	1.5700	628.2041	0.44
56	1.2771	511.0060	0.89
57	1.2650	506.1645	1.27
58	1.2495	499.9624	1.47
59	1.2415	496.7614	1.34
60	1.2252	490.2393	1.50
61	1.2080	483.3570	0.75
62	1.1949	478.1153	1.16
63	1.1787	471.6332	1.19
64	1.1658	466.4716	1.19
65	1.1535	461.5500	0.65
66	1.1486	459.5893	0.65
67	0.7164	286.6531	0.69
68	0.6971	278.9306	1.02
69	0.6817	272.7686	0.86
70	0.6669	266.8467	0.91
71	0.6471	258.9241	0.57

32077-139
crystallized
nmr400c c-13





Current Data Parameters
NAME 32077-139
EXPNO 6
PROCNO 1

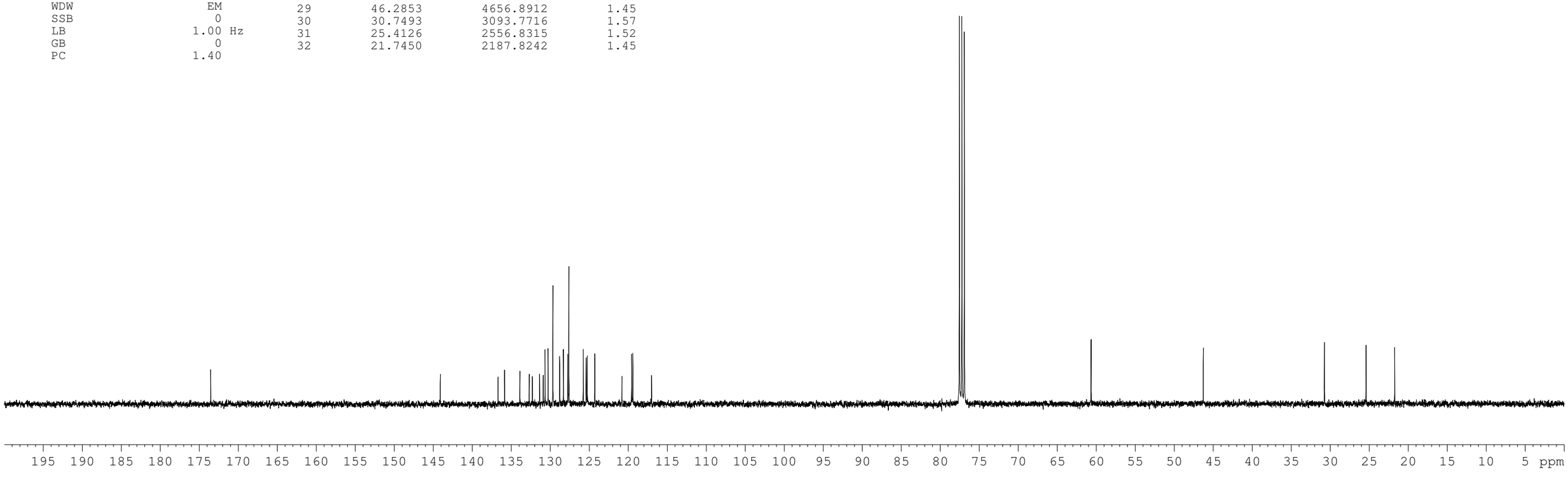
F2 - Acquisition Parameters
Date_ 20101218
Time 16.03
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 2006
DS 4
SWH 28248.588 Hz
FIDRES 0.431039 Hz
AQ 1.1600549 sec
RG 8192
DW 17.700 usec
DE 7.00 usec
TE 300.2 K
D1 0.10000000 sec
d11 0.03000000 sec
TD0 40

======== CHANNEL f1 ========
NUC1 13C
P1 2.60 usec
PL1 0.00 dB
SFO1 100.6228303 MHz

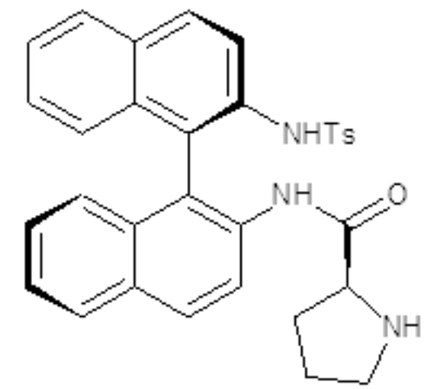
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 120.00 dB
PL12 17.00 dB
SFO2 400.1320007 MHz

F2 - Processing parameters
SI 32768
SF 100.6127485 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	173.5330	17459.6321	0.91
2	144.0836	14496.6470	0.79
3	136.7174	13755.5134	0.77
4	135.8742	13670.6767	0.89
5	133.9183	13473.8882	0.89
6	132.7197	13353.2938	0.79
7	132.3187	13312.9481	0.73
8	131.3941	13219.9215	0.80
9	130.9145	13171.6677	0.78
10	130.6976	13149.8448	1.40
11	130.2959	13109.4286	1.42
12	129.6877	13048.2359	2.98
13	128.8111	12960.0388	1.26
14	128.3332	12911.9560	1.41
15	127.7788	12856.1763	1.31
16	127.6379	12841.9999	3.50
17	125.7894	12656.0173	1.40
18	125.4174	12618.5893	1.24
19	125.2719	12603.9502	1.29
20	124.3088	12507.0500	1.32
21	120.8226	12156.2939	0.77
22	119.5787	12031.1417	1.30
23	119.4298	12016.1604	1.32
24	117.0429	11776.0079	0.77
25	77.5556	7803.0821	9.86
26	77.2377	7771.0973	10.00
27	76.9199	7739.1226	9.74
28	60.6700	6104.1755	1.65
29	46.2853	4656.8912	1.45
30	30.7493	3093.7716	1.57
31	25.4126	2556.8315	1.52
32	21.7450	2187.8242	1.45



(R_a,S)-diastereomer



32077-135
recrystallized R-Binam-Ts-L-pro
nmr500c h-1

Current Data Parameters
NAME 32077-135
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20101126
Time 12.24
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 4
SWH 13020.833 Hz
FIDRES 0.198682 Hz
AQ 2.5166707 sec
RG 228.1
DW 38.400 usec
DE 6.50 usec
TE 300.0 K
D1 0.10000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -4.00 dB
SFO1 500.1330885 MHz

F2 - Processing parameters
SI 32768
SF 500.1300079 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Peak	?(F1) [ppm]	?(F1) [Hz]	Int
1	8.8073	4404.7950	4.58
2	8.7892	4395.7427	4.85
3	8.1626	4082.3612	4.19
4	8.1445	4073.3088	5.28
5	8.0667	4034.3987	3.59
6	8.0486	4025.3464	3.42
7	7.9993	4000.6900	3.90
8	7.9812	3991.6376	3.16
9	7.9166	3959.3292	2.63
10	7.9001	3951.0771	3.04
11	7.8946	3948.3264	2.82
12	7.8780	3940.0242	2.76
13	7.4139	3707.9139	1.48
14	7.4123	3707.1137	1.52
15	7.3988	3700.3619	3.75
16	7.3850	3693.4601	3.92
17	7.3714	3686.6583	1.91
18	7.3693	3685.6081	1.99
19	7.3629	3682.4072	6.18
20	7.3463	3674.1051	6.73
21	7.2702	3636.0452	4.10
22	7.2335	3617.6904	1.49
23	7.2313	3616.5901	1.49
24	7.2197	3610.7886	1.57
25	7.2171	3609.4883	2.43
26	7.2145	3608.1879	1.74
27	7.2030	3602.4364	1.49
28	7.2008	3601.3362	1.36
29	7.0224	3512.1130	5.29
30	7.0063	3504.0609	4.93
31	6.9956	3498.7095	1.64
32	6.9935	3497.6592	1.56
33	6.9792	3490.5074	2.55
34	6.9768	3489.3070	1.67
35	6.9650	3483.4055	1.54
36	6.9628	3482.3052	1.44
37	6.9224	3462.1000	2.81
38	6.9054	3453.5978	2.49
39	6.5473	3274.5012	2.80
40	6.5305	3266.0990	2.56
41	3.5188	1759.8575	1.70
42	3.5098	1755.3563	1.88
43	3.5000	1750.4550	1.86
44	3.4910	1745.9539	1.78
45	2.6232	1311.9410	0.79
46	2.6090	1304.8392	1.57
47	2.6035	1302.0885	1.07
48	2.5949	1297.7874	1.04
49	2.5892	1294.9366	1.81
50	2.5751	1287.8848	0.98
51	2.3449	1172.7549	20.00
52	2.3353	1167.9536	2.20
53	2.3268	1163.7025	1.33
54	2.3230	1161.8020	1.40
55	2.3150	1157.8010	1.51
56	2.3031	1151.8494	0.99
57	1.9986	999.5598	0.71
58	1.9889	994.7086	0.69
59	1.9803	990.4075	0.77
60	1.9727	986.6065	1.27
61	1.9546	977.5541	1.19
62	1.9385	969.5020	0.69
63	1.9022	951.3473	1.00
64	1.8991	949.7969	0.93
65	1.8885	944.4955	1.24
66	1.8783	939.3942	1.10
67	1.8634	931.9423	0.67
68	1.5496	775.0015	0.82
69	1.5435	771.9507	0.68
70	1.5385	769.4500	1.40
71	1.5357	768.0497	1.28
72	1.5279	764.1486	1.88
73	1.5249	762.6482	2.03
74	1.5141	757.2468	2.38
75	1.4995	749.9449	1.56