Electronic Supplementary Material (ESI) for Chemical Communications

Stereochemical Liability of Azatitanacyclopropanes: Dynamic Kinetic Resolution in Reductive Cross-Coupling Reactions with Allylic Alcohols

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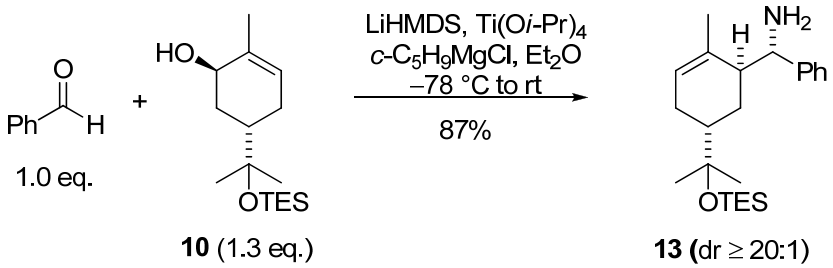
Supporting Information

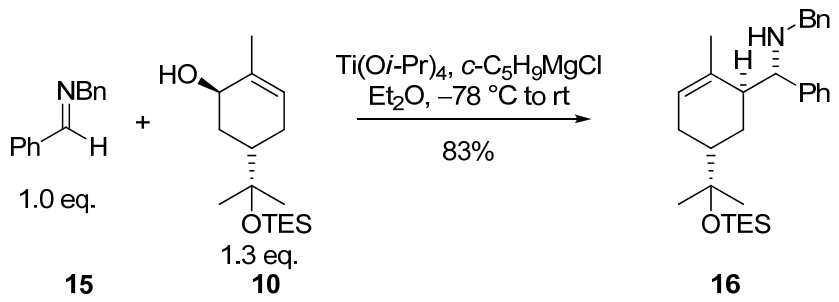
General Information: All reactions were carried out in flame-dried flasks under an atmosphere of dry argon unless otherwise specified. Dichloromethane was dried over activated alumina columns and sparged with argon prior to use. Diethyl ether and tetrahydrofuran were dried and distilled from sodium-benzophenone. Ti(O*i*-Pr)$_4$ (Aldrich, 97%) was distilled prior to use (69-70 °C, < 1 Torr). *i*-PrMgCl (Aldrich) was titrated by the method of Love *et al*.[1] *trans*-*p*-Menth-6-ene-2,8-diol was purchased from Aldrich and used without purification. Enantiomeric excess of chiral alcohols **4, 18** and **20** were determined by using Mosher's ester analysis.[2] Enantiomeric excess of amines **14, 17, 19** and **21** were determined by using Mosher's amide analysis.[3] All other solvents and reagents were used as received from commercial suppliers. Thin-layer chromatography was performed on 250 μm E. Merck silica gel plates (60F-254). Flash column chromatography was performed using Silicycle SiliaFlash P60 silica gel, 40-63 μm particle size. ^{1}H NMR data were recorded at 400 MHz on a Bruker AM-400 in CD_3Cl. ^{13}C NMR data were recorded at 100 MHz on a Bruker AM-400. Infrared spectra were recorded on a PerkinElmer SpectrumOne FT-IR instrument. LRMS spectra were acquired on a Varian 500-MS mass spectrometer under soft ionization mode.



Preparation of (*S*)-((1*S*,5*R*)-2-methyl-5-(2-(triethylsilyloxy)propan-2-yl)cyclohex-2-enyl)(phenyl)methanamine (13): To a solution of 106 mg (1.0 mmol) of benzaldehyde in 5 mL of anhydrous ether was added 1.0 mL (1.0 mmol) of 1.0 M LiHMDS in THF at −10 °C under argon. The reaction mixture initially appeared milky, then turned into a clear pale yellow solution. After 20 min, a solution of 0.45 mL (0.426 g, 1.5 mmol) of Ti(O*i*-Pr)$_4$ in 10 mL of anhydrous ether was added via a syringe. After stirring for 5 min, the reaction mixture was cooled to −78 °C, and 1.5 mL (3.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The reaction temperature was raised to −30 °C over 30 min, and kept at −30 °C for 1 h, resulting in a black suspension. Next, a solution of the lithium alkoxide of alcohol **10** in 4 mL of THF, prepared by deprotonation of 369 mg (1.3 mmol) of alcohol **10**[4] at −78 °C with 0.5 mL (1.3 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the black suspension via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 48 h. Finally, sequential addition of 10 mL of diethyl ether and 5 mL of sat. aq. $NaHCO_3$ was followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 10 mL of diethyl ether (2×). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (ethyl acetate : hexanes = 1:10, 220 ml; 1:2, 240 mL) to give 330 mg (87%, d.r. ≥ 20:1) of homoallylic amine **13** as a colorless oil. No evidence for minor isomer was observed by ^{1}H NMR. The assignment of relative stereochemistry was based on our previous study.[4]

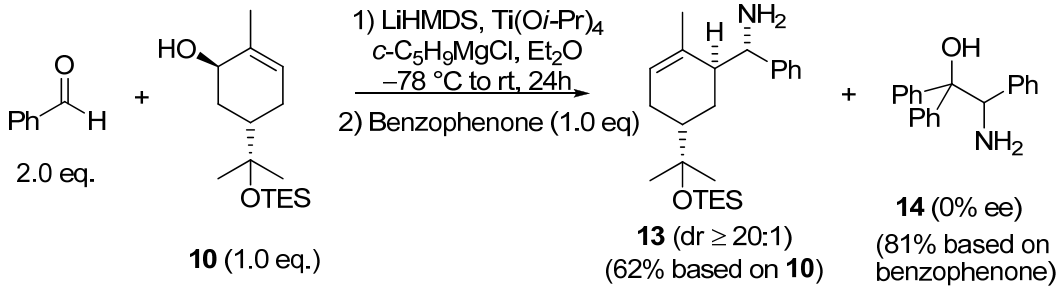
Data for amine **13**: IR (neat) 3029, 2910, 2874, 1563, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.53 (q, *J* = 6.8 Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.91 (t, *J* = 6.8 Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 1.00 (d, *J* = 3.2 Hz, 6H, CH_3), 1.07 (m, 1H), 1.18 (m, 1H), 1.63 (s, 2H, NH_2), 1.66 (s, 1H), 1.80 (m, 1H), 1.93 (m, 1H), 1.97 (s, 3H, CH_3), 2.32 (t, *J* = 6.0 Hz, 1H), 4.17 (d, *J* = 6.4

Hz, 1H, $CHNH_2$), 5.59 (s, 1H, =CH), 7.28-7.33 (m, 5H, Ph-); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.79, 7.17, 24.61, 25.61, 26.64, 27.16, 27.84, 39.88, 46.94, 58.78, 74.85, 125.42, 126.78, 126.89, 128.11, 134.06, 145.29; LRMS $C_{23}H_{40}NOSi$ + H^+ calcd *m*/*z* 374.3, found *m*/*z* 374.0.



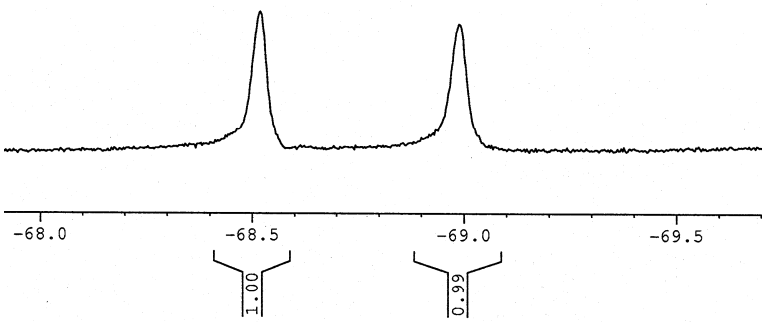
Preparation of (*S*)-*N*-benzyl-1-((1*S*,5*S*)-2-methyl-5-(2-(triethylsilyloxy)propan-2-yl)cyclohex-2-enyl)-1-phenylmethanamine (16): To a solution of 195 mg (1.0 mmol) of imine 1**5** in 5 mL of anhydrous ether was added a solution of 0.45 mL (0.426 g, 1.5 mmol) of Ti(O*i*-Pr)$_4$ in 10 mL of anhydrous ether via a syringe. After stirring for 5 min, the reaction mixture was cooled to −78 °C, and 1.5 mL (3.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The reaction temperature was raised to −30 °C over 30 min, and kept at −30 °C for 1 h, resulting in a black suspension. Next, a solution of the lithium alkoxide of alcohol **10** in 4 mL of THF, prepared by deprotonation of 369 mg (1.3 mmol) of alcohol **10**[4] at −78 °C with 0.5 mL (1.3 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the black suspension via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 24 h. Finally, sequential addition of 10 mL of diethyl ether and 5 mL of sat. aq. $NaHCO_3$ was followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 10 mL of diethyl ether (2×). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (ethyl acetate : hexanes = 1:10, 220 ml; 1:5, 180 mL) to give 380 mg (82%, d.r. ≥ 20:1) of homoallylic amine **16** as a colorless oil.

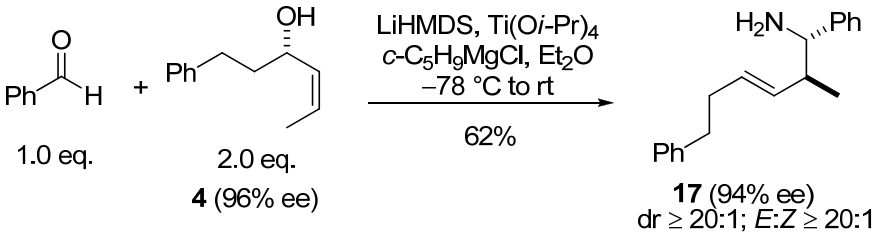
Data for amine **16**: IR (neat) 3325, 3063, 2911, 2874, 1603, 1494, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.53 (q, *J* = 6.8 Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.93 (t, *J* = 6.8 Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 1.01 (d, *J* = 3.2 Hz, 6H, CH_3), 1.02 (m, 1H), 1.19 (m, 1H), 1.65 (s, 1H, NH_2), 1.73 (m, 1H), 1.82 (m, 1H), 1.90 (m, 1H), 1.99 (s, 3H, CH_3), 2.36 (t, *J* = 6.0 Hz, 1H), 3.58 and 3.69 (ABq, *J* = 13.2 Hz, 2H, -$C\underline{H}_2$Ph), 3.86 (d, *J* = 6.4 Hz, 1H, $CHNH_2$), 5.57 (s, 1H, =CH), 7.28-7.35 (m, 10H, Ph-); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.82, 7.19, 24.65, 25.94, 26.58, 27.17, 27.89, 39.84, 46.24, 52.01, 65.39, 74.86, 125.31 126.70, 126.77, 127.85, 128.02, 128.08, 128.26, 134.14, 140.98, 143.14; LRMS $C_{30}H_{46}NOSi$ + H^+ calcd *m*/*z* 464.3, found *m*/*z* 464.4.



Dynamic behavior of azametallocyclopropane observed after simple kinetic resolution: To a solution of 212 mg (2.0 mmol) of benzaldehyde in 10 mL of anhydrous ether was added 2.0 mL (2.0 mmol) of 1.0 M LiHMDS in THF at −10 °C under argon. The reaction mixture initially appeared milky, then turned into a clear pale yellow solution. After 20 min, a solution of 0.9 mL (0.852 g, 3.0 mmol) of $Ti(O\textit{i}\text{-}Pr)_4$ in 10 mL of anhydrous ether was added via a syringe. After stirring for 5 min, the reaction mixture was cooled to −78 °C, and 3.0 mL (6.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The reaction temperature was raised to −30 °C over 30 min, and kept at −30 °C for 1 h, resulting in a black suspension. Next, a solution of the lithium alkoxide of alcohol **10** in 4 mL of THF, prepared by deprotonation of 285 mg (1.0 mmol) of alcohol **10**[4b] at −78 °C with 0.4 mL (1.0 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the black suspension via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 24 h. After cooling back to

−30 °C, a solution of 182 mg (1.0 mmol) of benzophenone in 2 mL of anhydrous ether was added to the reaction mixture via a syringe. The resulting dark brown mixture was allowed to rise to rt and stirred for 3 hours before sequential addition of 10 mL of diethyl ether and 5 mL of sat. aq. $NaHCO_3$. After a vigorous stirring for 1 h, the aqueous phase of the mixture was separated and extracted with 10 mL of diethyl ether (2×). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (ethyl acetate : hexanes = 1:10, 220 ml; 1:2, 240 mL) to give 231 mg (62% based on **10**, d.r. ≥ 20:1) of homoallylic amine **13** and 233 mg (81% based on benzophenone) of hydroxyl amine **14** as a white solid.[5] ^{19}F NMR of hydroxylamine **14** derivative (shown below) indicates it to be racemic.



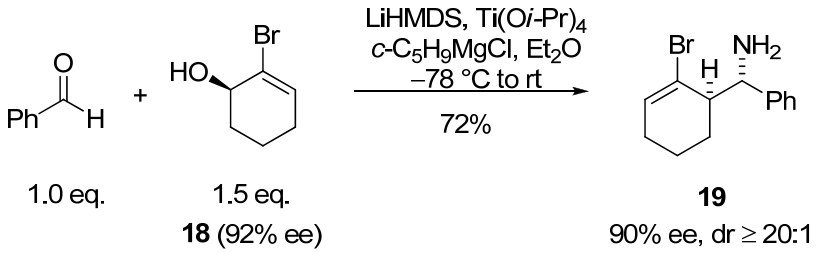


1.0 eq. 2.0 eq. **4** (96% ee)

17 (94% ee)
dr ≥ 20:1; *E*:*Z* ≥ 20:1

Preparation of (1*S*,2*S*,*E*)-2-methyl-1,6-diphenylhex-3-en-1-amine (17): To a solution of 106 mg (1.0 mmol) of benzaldehyde in 5 mL of anhydrous ether was added 1.0 mL (1.0 mmol) of 1.0 M LiHMDS in THF at −10 °C under argon. The reaction mixture initially appeared milky, then quickly became a clear pale yellow solution. After 20 min, a solution of 0.46 mL (0.426 g, 1.5 mmol) of Ti(O*i*-Pr)$_4$ in 10 mL of anhydrous ether was added via a syringe. After stirring for 5 min, the solution was cooled to −78 °C, and 1.5

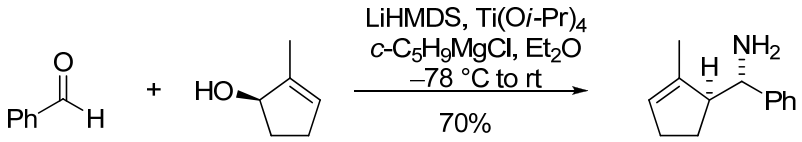
mL (3.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The temperature of the solution was raised to −40 °C over 30 min, then the solution was stirred at −40 °C for an additional 1.5 h, resulting in a dark brown suspension. Next, a solution of the lithium alkoxide of alcohol **4** in 4 mL of THF, prepared by deprotonation of 356 mg (2.0 mmol, 96% ee by Mosher's ester) of alcohol **4**[6] at −78 °C with 0.8 mL (2.0 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then was stirred for 12 h. Finally, sequential addition of 10 mL of diethyl ether and 5 mL of saturated aqueous $NaHCO_3$ was followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 10 mL of diethyl ether (2×). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (CH_2Cl_2:MeOH:NH_4OH = 400:10:1) to give 164 mg (62%, 94% ee, d.r. ≥ 20:1, *E*:*Z* ≥ 20:1) of homoallylic amine **17**[6] as a colorless oil.



Preparation of (*S*)-((*R*)-2-bromocyclohex-2-enyl)(phenyl)methanamine (19): To a solution of 106 mg (1.0 mmol) of benzaldehyde in 5 mL of anhydrous ether was added 1.0 mL (1.0 mmol) of 1.0 M LiHMDS in THF at −10 °C under argon. The reaction mixture initially appeared milky, then turned into a clear pale yellow solution. After 20 min, a solution of 0.45 mL (0.426 g, 1.5 mmol) of Ti(O*i*-Pr)$_4$ in 5 mL of anhydrous ether was added via a syringe. After stirring for 5 min, the reaction mixture was cooled to −78 °C, and 1.5 mL (3.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The reaction temperature was raised to −30 °C over 30 min, and kept at −30 °C for 1 h, resulting in a black suspension. Next, a solution of the lithium

alkoxide of alcohol **18** in 4 mL of THF, prepared by deprotonation of 264 mg (1.5 mmol, 92% *ee*) of alcohol **18**[7] at −78 °C with 0.6 mL (1.5 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the black suspension via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 24 h. Finally, sequential addition of 10 mL of diethyl ether and 5 mL of sat. aq. $NaHCO_3$ was followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 10 mL of diethyl ether (2×). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (ethyl acetate : hexanes = 1:10, 220 ml; 1:2, 240 mL) to give 190 mg (72%, 90% ee, d.r. ≥ 20:1) of homoallylic amine **19** as a colorless oil. The assignment of relative stereochemistry was based on our previous study.[4]

Data for amine **19**: IR (neat) 3375, 3060, 2931, 2866, 1638, 1602, 1494, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.68 (m, 1H), 1.13 (m, 1H), 1.52 (m, 2H), 1.54 (s, 2H, NH_2), 1.59 (m, 1H), 1.80 (m, 1H), 2.52 (m, 1H, =C(Br)C<u>H</u>), 4.50 (d, *J* = 6.4 Hz, 1H, $CHNH_2$), 6.18 (m, 1H, =CH), 7.11-7.29 (m, 5H, Ph-); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.09, 24.72, 27.55, 49.51, 56.81, 125.15, 126.96, 127.03, 128.05, 132.65, 142.79; LRMS $C_{13}H_{17}BrN$ + H^+ calcd *m*/*z* 266.1 and 268.1, found *m*/*z* 266.0 and 268.0.



1.0 eq. 1.5 eq. **20** (94% ee)

21
91% ee, dr ≥ 20:1

Preparation of (*S*)-((*S*)-2-methylcyclopent-2-enyl)(phenyl)methanamine (21): To a solution of 106 mg (1.0 mmol) of benzaldehyde in 5 mL of anhydrous ether was added 1.0 mL (1.0 mmol) of 1.0 M LiHMDS in THF at −10 °C under argon. The reaction mixture initially appeared milky, then turned into a clear pale yellow solution. After 20 min, a solution of 0.45 mL (0.426 g, 1.5 mmol) of Ti(O*i*-Pr)$_4$ in 5 mL of anhydrous ether was added via a syringe. After stirring for 5 min, the reaction mixture was cooled to −78 °C, and 1.5 mL (3.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a

syringe over 2 min. The reaction temperature was raised to −30 °C over 30 min, and kept at −30 °C for 1 h, resulting in a black suspension. Next, a solution of the lithium alkoxide of alcohol **20** in 4 mL of THF, prepared by deprotonation of 147 mg (1.5 mmol, 94% *ee*) of alcohol **20**[8] at −78 °C with 0.6 mL (1.5 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the black suspension via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 24 h. Finally, sequential addition of 10 mL of diethyl ether and 5 mL of sat. aq. $NaHCO_3$ was followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 10 mL of diethyl ether (2×). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (ethyl acetate : hexanes = 1:10, 220 ml; 1:2, 240 mL) to give 131 mg (70%, 91% ee, d.r. ≥ 20:1) of homoallylic amine **21** as a colorless oil. The assignment of relative stereochemistry was based on our previous study.[4]

Data for amine **21**: IR (neat) 3286, 3030, 2927, 2852, 1648, 1547, 1495, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.65 (m, 1H), 1.68 (s, 3H, CH_3), 1.82 (m, 3H), 1.88 (br, 2H, NH_2), 2.78 (m, 1H, =C(Me)C<u>H</u>), 4.01 (d, *J* = 4.8 Hz, 1H, C<u>H</u>NH_2), 5.29 (t, *J* = 1.2 Hz, 1H, =CH), 7.14-7.26 (m, 5H, Ph-); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.58, 27.41, 30.87, 55.83, 57.68, 126.58, 126.82, 127.56, 127.81, 140.40, 144.37; LRMS $C_{13}H_{18}N + H^+$ calcd *m*/*z* 188.1, found *m*/*z* 188.0.

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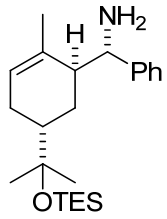
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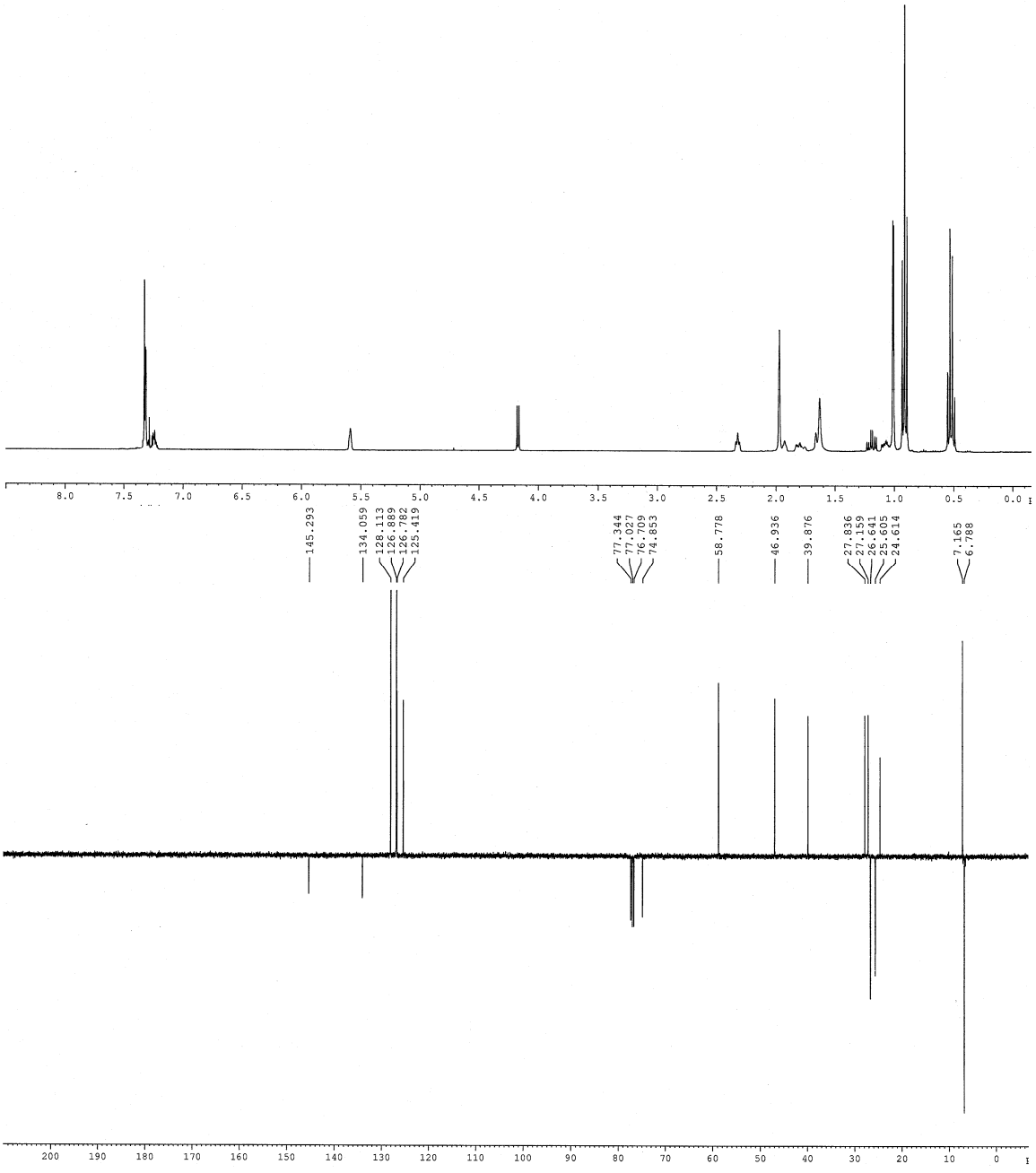
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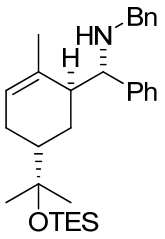
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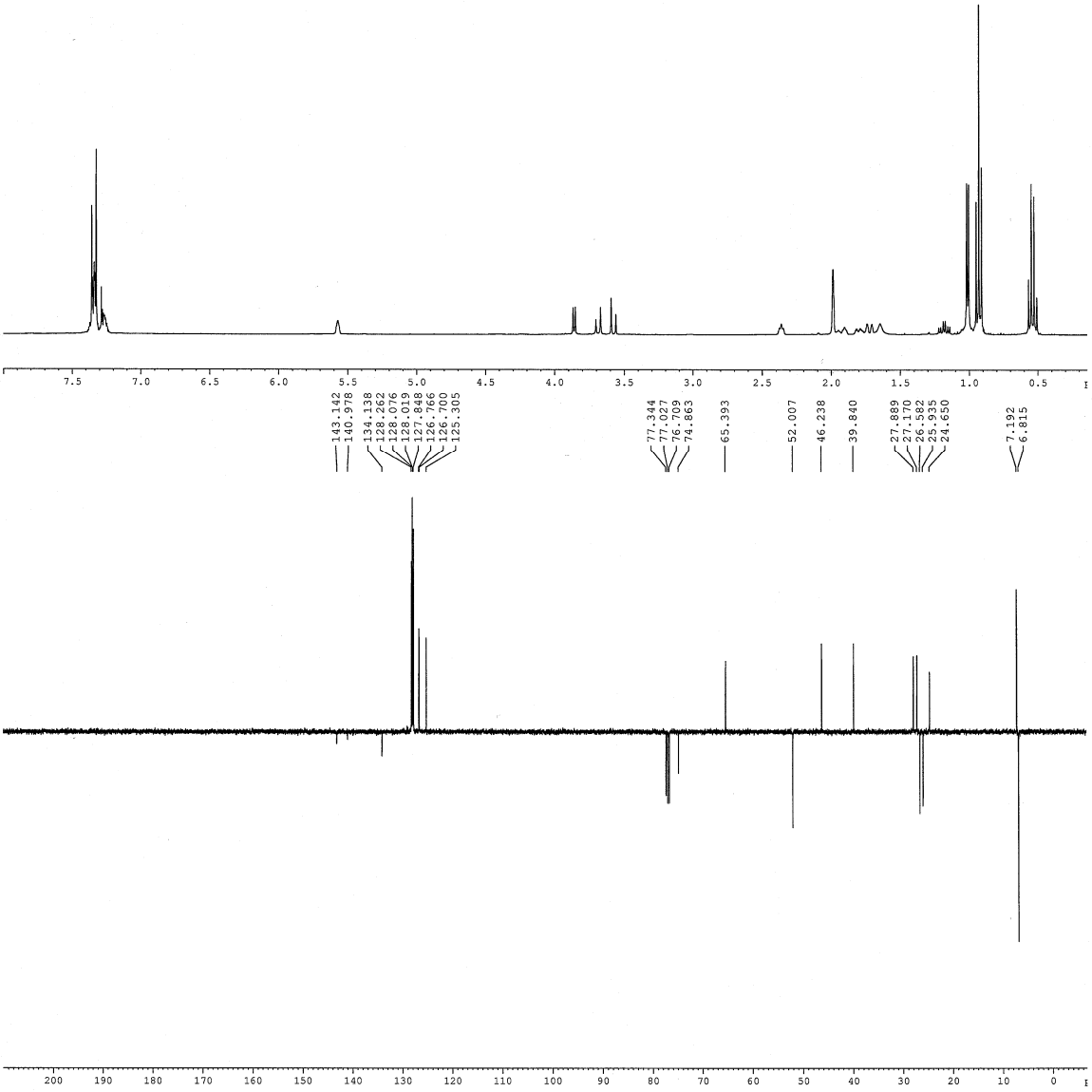
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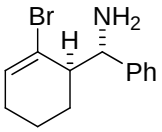
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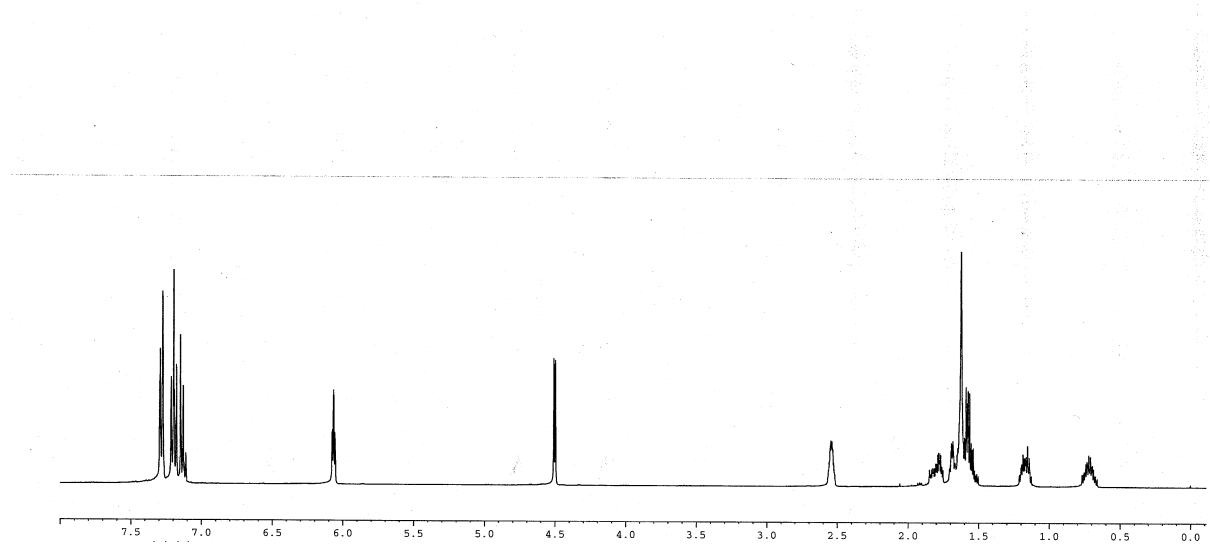
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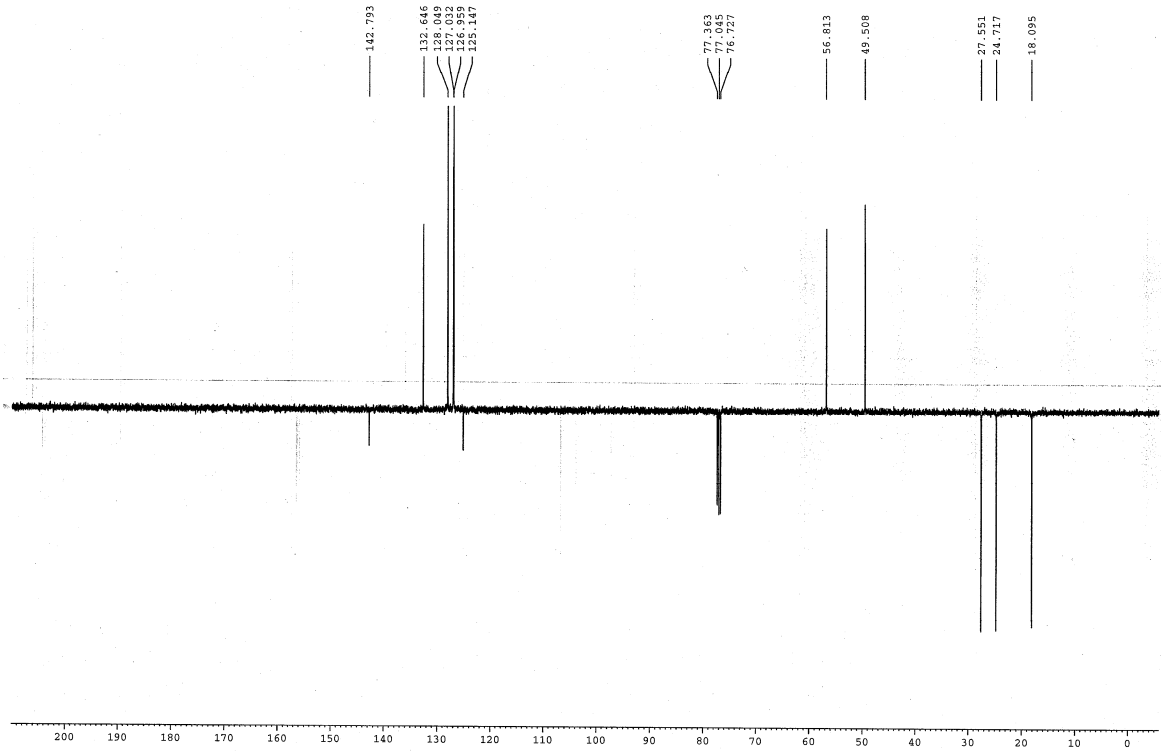
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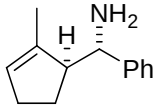
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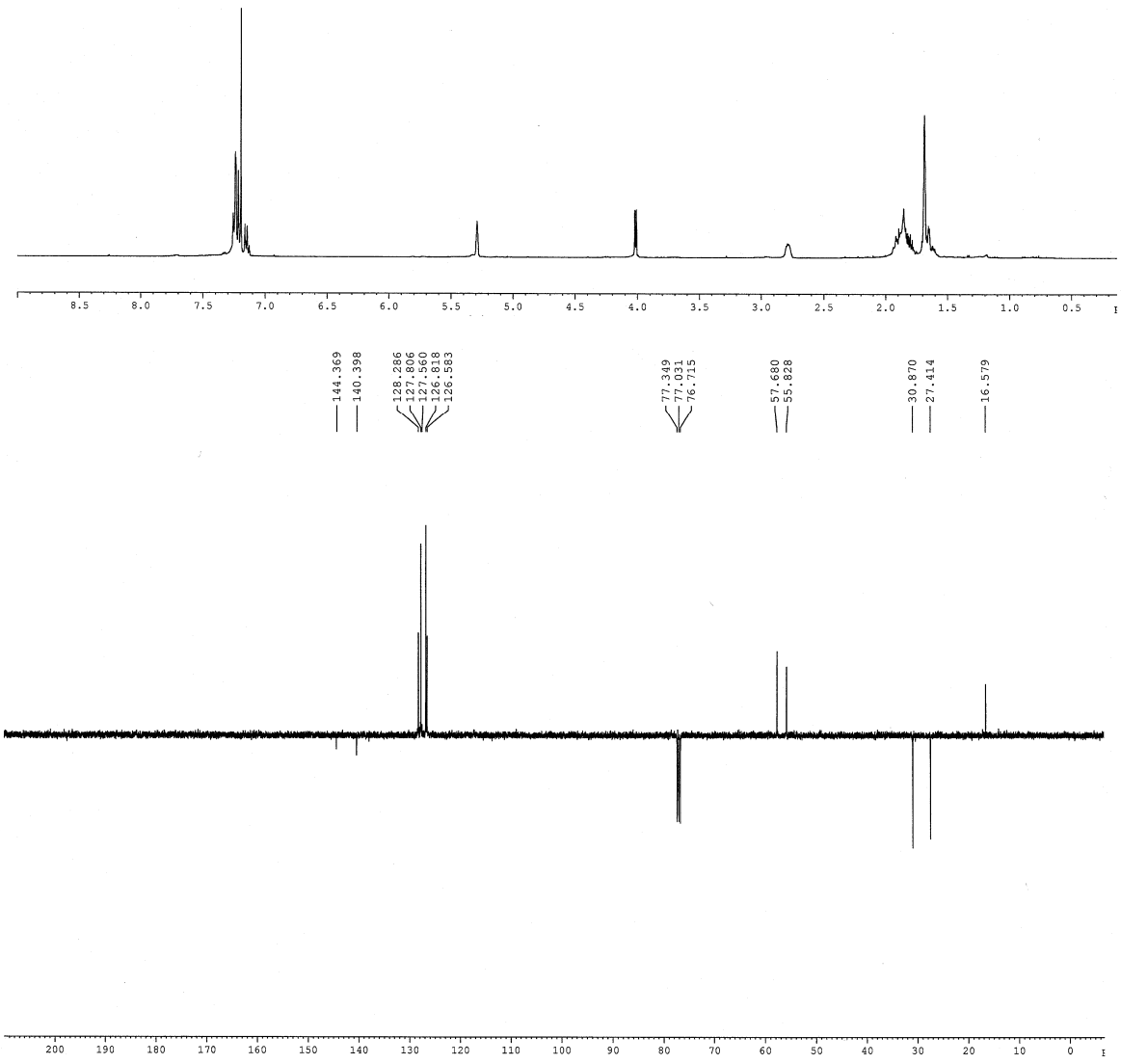
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16.579