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Synthesis of cis-(N-(pyridin-4-ylmethyl)-2-(3-(m-tolyloxy)cyclohexyl)propan-1-amine)

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We use this protocol and it's working

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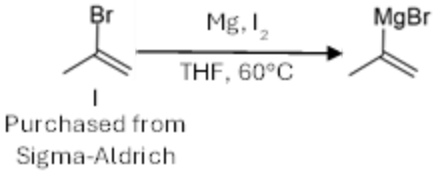
Abstract

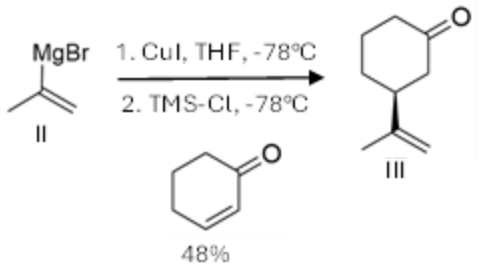
This protocol is for the synthesis of cis-(N-(pyridin-4-ylmethyl)-2-(3-(m-tolyloxy)cyclohexyl)propan-1-amine) (c458)

1 **Preparation of prop-1-en-2-ylmagnesium bromide**



6.2 g magnesium turnings (252.6 mmol, 1.05 equiv.) were suspended in 500 mL dry tetrahydrofuran in a one liter flask fitted with a magnetic stirring bar and a N_2 inlet. 5 mL isopropenyl bromide (57.2 mmol, 0.24 equiv.) and a small iodine crystal (~1 mm dia.) were added, and the mixture was heated to 60 °C. The reaction initiated in about fifteen minutes. The heating bath was then turned off and 16 mL isopropenyl bromide (182.9 mmol, 0.76 equiv.) was added in 4 mL portions. The vigorous reaction was allowed to subside in between additions. The resulting pale-yellow solution of prop-1-en-2-ylmagnesium bromide was allowed to cool to room temperature and used in the next step. The theoretical concentration of the
solution is 0.48 M. Only a trace amount of undissolved magnesium remained.

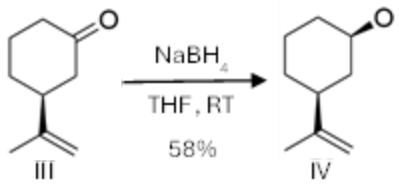
2 **Preparation of 3-(prop-1-en-2-yl)cyclohexan-1-one**



11.4 g copper iodide (60.0 mmol, 0.6 equiv.) was slurried in 750 mL of anhydrous tetrahydrofuran and
chilled in a dry ice- acetone bath. 250 mL compound **II** (0.48M in tetrahydrofuran, 120 mmol, 1.2 equiv.) was added dropwise over the course of one hour to the copper iodide slurry. The temperature was kept below -70 °C during the addition. 9.6 g Cyclohexen-1-one (100.0 mmol, 1.0 equiv.) and 15.2 mL chlorotrimethylsilane (120.0 mmol, 1.2 equiv.) were dissolved in 50 mL of dry tetrahydrofuran. The resulting solution was added dropwise over the course of 45 minutes to the chilled alkyl copper slurry. The mixture was stirred for an additional fifteen minutes, then thin layer chromatography (TLC) using

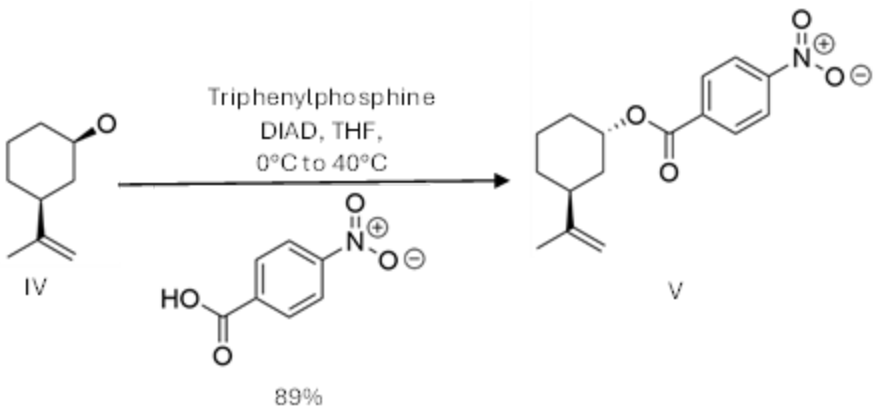
30%
ethyl acetate in hexane revealed a mixture of desired product, some unreacted cyclohexen-1-one, and two minor side products. The reaction was quenched with 250 mL of saturated ammonium chloride solution. The cold bath was then removed, and the slurry was allowed to warm to approximately 5 °C and was poured into a mixture of 50 mL 30% ammonium hydroxide dissolved in 2.5 L of water. The mixture was extracted with 1L ethyl acetate three times, discarding the aqueous phase. The combined organic phases were then extracted with 1L brine two times, discarding the aqueous phase. The organic phase was concentrated to approximately 200 mL using a rotary evaporator (25 mm Hg, bath temperature 20 °C), then diluted to approximately 1 L with diethyl ether and dried over sodium sulfate. The solids
were removed by filtration and discarded, then the mother liquor was concentrated to obtain an orange oil that was purified using a CombiFlash (330 g column, 0-10% ethyl acetate in hexane, 1 h) to obtain Compound **III** as a pale-yellow oil Yield: 6.6 g (48% from **II**).

3 **Preparation of cis-3-(prop-1-en-2-yl)cyclohexan-1-ol IV**



11.8 g compound **III** (85.4 mmol, 1.0 equiv.) was dissolved in 300 mL of tetrahydrofuran. 9.7 g Sodium borohydride (256.1 mmol, 3.0 equiv.) was added, and the resulting mixture was stirred at room temperature, and was determined to be complete after two hours by TLC using 30% ethyl acetate in hexane. The reaction was quenched with a minimal amount of 3 M aqueous hydrochloric acid until the pH was approximately 2. The solids were filtered and discarded, and the mother liquor was concentrated to oil using a rotary evaporator (25 mm Hg, bath temperature 20 °C). The oil was diluted with 500 mL diethyl ether and dried over sodium sulfate. The solids were removed by filtration and discarded, and the mother liquor was concentrated to obtain a yellow oil. The material was combined with a previous batch (14 g scale) and purified using a CombiFlash (330 g column, 0-20% ethyl acetate in hexane, 1 h) to obtain Compound **IV** as a pale-yellow oil. Yield: 13.6 g cis isomer and 1.5 g trans isomer (58% from **III**).

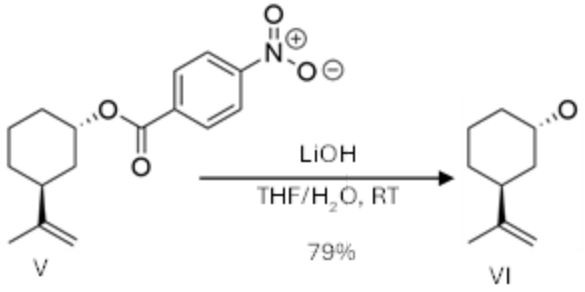
4 **Preparation of Compound trans-3-(prop-1-en-2-yl)cyclohexyl 4-nitrobenzoate V**



Note: this procedure was carried out with 9.5 g of Compound IV, split into two 4.75 g batches that were run in parallel.

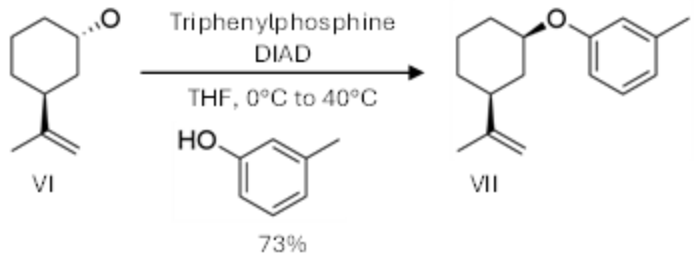
4.75 g compound **IV** (33.9 mmol, 1.0 equiv.) was dissolved in 250 mL tetrahydrofuran, as well as 22.6 g 4-nitrobenzoic acid (135.5 mmol, 4.0 equiv.) and 35.5 g triphenylphosphine (135.5 mmol, 4.0 equiv.). The resulting solution was chilled in an ice water bath, then 26.7 mL N, N′-diisopropylazodicarboxylate (135.5 mmol, 4.0 equiv.) was added in small portions over a one-hour period, taking care to keep the temperature below 10 °C during the addition. The ice bath was removed, and the reaction was stirred for fifteen hours at room temperature, then at 40 °C for three hours. After cooling to room temperature, the reaction was diluted with 250 mL diethyl ether and extracted with 150 mL saturated sodium bicarbonate solution two times. The combined aqueous phases were back extracted with 150 mL diethyl ether. The aqueous phase was discarded, and the combined organics were dried over sodium sulfate. The solids were filtered and discarded, and the mother liquor was concentrated to obtain a yellow semisolid. At this point, the material from both batches were combined and suspended in 100 mL diethyl ether and allowed to sit overnight at room temperature. The resulting slurry was diluted with 50 mL diethyl ether and 150 mL hexane, and the solids were removed by filtration and discarded. The mother liquor was concentrated to obtain a yellow oil that was split into three portions and purified by CombiFlash (330 g column, 0 - 15% ethyl acetate in hexane, 1 h) to obtain 17.4 g pale yellow solid (Compound **V**). Yield: 89%.

5 **Preparation of Compound trans-3-(prop-1-en-2-yl)cyclohexan-1-ol VI**



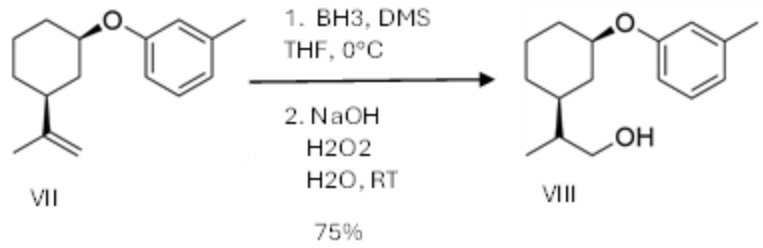
17.4 g compound **V** (60.1 mmol, 1.0 equiv.) was dissolved in 100 mL of tetrahydrofuran. A solution of 4.3 g lithium hydroxide (180.3 mmol, 3.0 equiv.) dissolved in 50 mL of water was added, and the resulting solution was stirred at room temperature. TLC using 20% ethyl acetate in hexane at 30 min showed mostly ester and very little product. 50 mL of tetrahydrofuran was added to improve solubility, and stirring at room temperature was resumed. TLC at 45 min using 20% ethyl acetate in hexane showed little change. A solution of 2.2 g lithium hydroxide (approx. 1.5 equiv.) dissolved in 25 mL water was added. TLC using 20% ethyl acetate in hexane at one hour showed little change. A solution of 2.2 g lithium hydroxide (approx. 1.5 equiv.) dissolved in 50 mL water and 50 mL tetrahydrofuran was added. The mixture was stirred for 15 h and was determined to be complete by TLC using 20% ethyl acetate in hexane. 600 mL of diethyl ether was added to the reaction and transferred to a separatory funnel. The organic phase was removed and retained. The aqueous phase was extracted with 100 mL of diethyl ether twice. The aqueous phase was discarded, and the combined organics were dried over sodium sulfate. The solids were removed by filtration and discarded, and the mother liquor was concentrated on a rotary evaporator (25 mm Hg, bath temperature 20 °C) to a yellow oil, which was dissolved in 50 mL of dichloromethane and filtered through a 1 cm deep silica gel pad. The pad was rinsed with a little additional dichloromethane, and the combined organics were concentrated on a rotary evaporator (25 mm Hg, bath temperature 20 °C) to obtain a pale-yellow oil that was purified by CombiFlash (120 g column, 0 - 20% ethyl acetate in hexane, 1 h) to obtain 6.7 g Compound **VI** as a colorless oil. Yield: (79%).

6 **Preparation of cis-1-(3-tolyloxy)-3-isopropenyl-cyclohexane VII**



4.75 g compound **IV** (33.9 mmol, 1.0 equiv.) was dissolved in 250 mL tetrahydrofuran, as well as 14.2 mL m-cresol (135.5 mmol, 4.0 equiv.) and 35.5 g triphenylphosphine (135.5 mmol, 4.0 equiv.). The resulting solution was chilled in an ice water bath, then 26.7 mL N, N'-diisopropylazodicarboxylate (135.5 mmol, 4.0 equiv.) was added in small portions over a one-hour period, taking care to keep the temperature below 10 °C during the addition. The ice bath was removed, and the reaction was stirred for 15 h at room temperature, then at 40 °C for three hours. After cooling to room temperature, the reaction was diluted with 250 mL diethyl ether and extracted with 150 mL saturated sodium bicarbonate solution twice. The combined aqueous phases were back extracted with 150 mL diethyl ether. The aqueous phase was discarded, and the combined organics were dried over sodium sulfate. The solids were filtered and discarded, and the mother liquor was concentrated to obtain an orange oil, which was dissolved in 150 mL of 1:1 diethyl ether/ hexane and stirred at room temperature for one hour. The solids were removed by filtration and discarded. The mother liquor was concentrated to obtain an orange oil that was purified by CombiFlash (330 g column, 0- 10% ethyl acetate/hexane, 1 h) to obtain 5.7 g pale oil (Compound **VII**). Yield: 73%.

7 **Preparation of cis-1-(3-methylphenyl)-3-(1-hydroxyprop-2-yl)cyclohexane VIII**

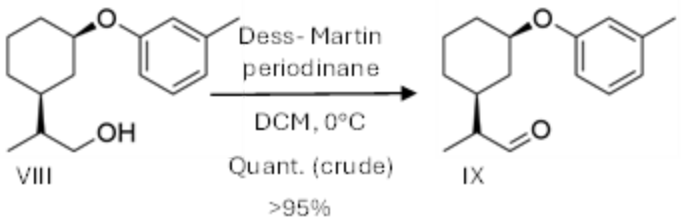


Note: this procedure was carried out with 5.7 g of Compound **VII**, split into three 1.9 g batches that were run in parallel.

1.9 g compound **VII** (8.2 mmol, 1.0 equiv.) was dissolved in 8.5 mL of dry tetrahydrofuran. The solution was chilled in an ice water bath, then a borane - dimethyl sulfide complex (2.0 M) in 4.1 mL tetrahydrofuran (8.2 mmol, 1.0 equiv.) was added dropwise over a 25-

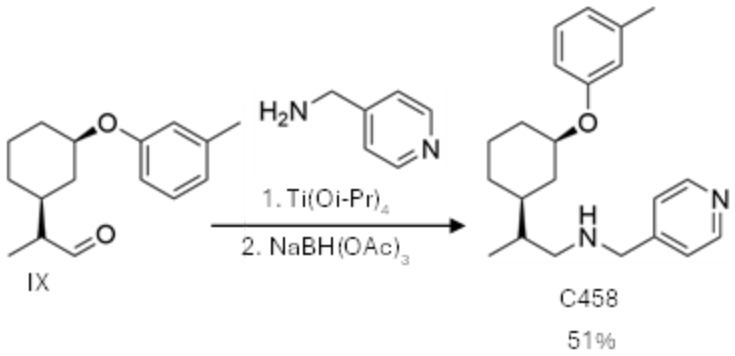
minute period. The resulting mixture was stirred in an ice water bath for three hours, then aqueous sodium hydroxide solution (3 M, 3.3 mL, 9.9 mmol, 1.2 equiv.) was added dropwise over a fifteen-minute period. 2.4 mL of aqueous hydrogen peroxide (35 wt. %, 29.5 mmol, 3.6 equiv.) was added over a five minute period, then the ice bath was removed, and the resulting mixture was stirred at room temperature. TLC using 20% ethyl acetate in hexane at fifteen minutes showed the starting material was consumed. The reaction was quenched with 1 M aqueous hydrochloric acid, extracted with 25 mL diethyl ether three times, discarding the aqueous phase. The combine organics were dried over sodium sulfate, the solids were removed by filtration and discarded, and the mother liquor was concentrated to an oil and purified by CombiFlash (80 g column, 0-30% ethyl acetate/hexane, 1 h) to obtain 5.4 g clear oil (Compound **VIII**). Yield: 75%.

8 **Preparation of cis-2-(-3-(m-tolyloxy)cyclohexyl)propanal IX**



50 mg compound **VIII** (201 mmol, and 1.0 equiv.) was dissolved in 0.75 mL dichloromethane: the resulting
solution was chilled in an ice water bath and 111 mg Dess-Martin periodinane (262 mmol, 1.3 equiv.) was added and the mixture was stirred in the ice water bath for two hours. TLC using 20% ethyl acetate in hexane showed the reaction was nearly complete, with a small trace of the remaining starting material. The mixture was stirred at room temperature for 30 minutes, then quenched with 1 mL sodium thiosulfate solution and extracted with 2 mL ethyl acetate twice. The combined organics were extracted with 2 mL of saturated sodium bicarbonate. The phases were separated, and the aqueous phase was back extracted with 4 mL of ethyl acetate. The combined organics were dried over sodium sulfate and the solids were removed by filtration and discarded. The mother liquor was concentrated on a rotary evaporator to obtain 50 mg of a yellow oil (Compound **IX**). The crude material was used without further purification in the next step.

9 **Preparation of cis-(N-(pyridin-4-ylmethyl)-2-(3-(m-tolyloxy)cyclohexyl)propan-1-amine)**



82 mg cis-2-(-3-(m-tolyloxy)cyclohexyl)propanal (0.33 mmol) was dissolved in 3 mL anhydrous THF. To this solution 51 µL of 4-(aminomethyl)pyridine (0.5 mmol) was added, followed by 202 µL of titanium tetraisopropoxide (0.67 mmol). The mixture was stirred at room temperature for 45 minutes, then cooled in an ice bath. 212 mg sodium triacetoxyborohydride (1 mmol) was added, and the ice bath was removed. After 45 minutes at room temperature, LC/MS analysis showed the reaction to be complete. The reaction was quenched with 1 M HCl and most of the solvent was removed under reduced pressure. The residue was dissolved in 1 mL DMSO and purified by HPLC to produce the title product (LC/MS = 339.2 $[M+H]^+$).

9.1 **Alternate Preparation of cis-(N-(pyridin-4-ylmethyl)-2-(3-(m-tolyloxy)cyclohexyl)-propan-1-amine)**

82 mg cis-2-(-3-(m-tolyloxy)cyclohexyl)propanal (0.33 mmol) was dissolved in 3 mL anhydrous dichloroethane. 51 µL of 4-(aminomethyl)pyridine (0.5 mmol) was added and the mixture was stirred at room temperature for 45 minutes, after which 212 mg sodium triacetoxyborohydride (1 mmol) was added and the reaction mixture was brought to reflux. After 45 minutes, LC/MS analysis showed the reaction to be complete. The reaction was quenched with 1 M HCl and most of the solvent was removed under reduced pressure. The residue was dissolved in 1 mL DMSO and purified by HPLC to produce the title product (LC/MS = 339.2 $[M+H]^+$).