Novel enantioselective synthesis of (*S*)-ketamine using chiral auxiliary and precursor Mannich base

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Abstract

Ketamine has been extensiely used as an anesthetic drug. For the asymmetric synthesis of (*S*)-ketamine, can be use to chiral auxiliaries such as *tert*-butanesulfinamide (TBSA). Condensation of TBSA with ketones provides *tert*-butanesulfinylimines in consistently high yields. The *tert*-butanesulfinyl group actuates the imine groups for the attack of some different groups of nucleophiles, prepare as a potent chiral directing group, and after nucleophilic addition is easily dissociated by intervention with acid solution. In this work, for reach to the 2- (*N*-piperidino methyl)-1-phenylcyclohexylamine (**1**), we started with the cyclohexanone and using Mannich reaction achived to an aminoketone (Scheme 1). Then, we made the sulfiniylamin (**2**) by the condensation of TBSA with aminoketone. In addition, $Ti(OEt)_4$ is effective for reach to *N*-*tert*-butanesulfinylketimine in 85% yield. At next, we provided a new chiral center (**3**) using Grignard reagent as nucleophile at −78 °C (80% yield). At after multistep, finally, the (*S*)-ketamine synthesized under ozonolize condition and gave the good yield and enantioselectivity (75% yield and 75% ee).

Keywords: (*S*)-ketamine, asymmetric synthesis, enantioselective synthesis, aminoketone, chiral auxiliary, *tert*-butanesulfinamide.

1. Introduction

Ketamine induces its anesthetic actuates by blocking the *N*-methyl-D-aspartate receptor (NMDAR) in the central nervous system (CNS). Ketamine hampers the NMDAR by binding both in the open channel and at an allosteric site.[1] The commercial ketamine is a racemic mixture of their enantiomers. The racemic ketamine was produced by Stevens through rearrangement of 1-[(2-chlorophenyl)(methylimino)methyl]cyclopentanol.[2-5] The (*S*)-ketamine is display to be more powerful with an about 3–4 fold anesthetic potency compared to (*R*)-ketamine. This relates to the higher binding attraction for the PCP-site of the NMDAR.[6]

Then, the synthesis of chiral amines is of great interest due to their prevalence in biologically active molecules. Therefore, development of an asymmetric synthesis for the (*S*)-ketamine is highly desirable. One of routes of asymmetric synthesis for preparation of chiral molecules is using chiral auxiliaries.[7] At present, many routes of asymmetric synthesis of (*S*)-ketamine were reported. Recently, Kiyooka et al. were presented two procedures for this propose.[8] At first procedure, the phenyllithium was reacted to chiral α-ketoketal bearing chiral auxiliary on a ketone group with 83% yield and 82% de. However, the reaction of 2-chlorophenyllithium did not perform in which this procedure was unfavorable for the (*S*)-ketamine. At second procedure, a different strategy was designed, which the chiral carbon of ketamine with a reduction step by (*S*)-BINAL-H catalyst, was obtained (>99% ee). Beside, Biermann et al. were presented a new method, the chirality induction prepared using Sharpless dihydroxylation and followed with Ritter reaction (Scheme 2). Finally, the obtained alcoholamine was converted to (*S*)-norketamine by Jones oxidation (=99% ee).[9]

As part of our ongoing research to find a new dependable procedure to (*S*)-ketamine, we applied a simple methodology, using nucleophilic 1,2-addition to obtained chiral imine from β-aminoketone. Mannich reaction represents easily obtainable intermediates for the synthesis of β-aminoketone compounds.[10] Mannich bases are very reactive; in fact, the reactivity of the bases accounts for several interesting properties. β-Aminoketones demonstrate an eminent group of compounds in pharmaceutical chemistry because of their various biological properties.[11] Also, they are useful building blocks for the synthesis of various medicinal. They can present as chiral ligands for asymmetric synthesis.[12] Herein, we reported, an auxiliary-based process for the asymmetric synthesis of chiral nitrogen-substituted carbon center in the cyclohexane ring, which proceeds through the addition of Grignard reagent to obtained imine of *N*-*tert*-butylsulfinylimine with good yields and diastereoselectivities (Scheme 3). During the past few years, one of main research lines has focused on the use of *N*-(*tert*-butylsulfinyl)imines in asymmetric synthesis.[13-15] *N*-*tert*-butanesulfinamides have been established to be highly effective chiral auxiliaries in the synthesis of various chiral amines by the virtue of their good diastereocontrol and readily cleavage.[16,17] We report here on the preparation of quaternary carbon by the addition of Grignard reagent to *N*-sulfinylimine derived from cyclic Mannich base. Tertiary carbinamine was obtained by addition of Grignard reagents to *N*-sulfinylketimines in high yields (80%) and with high diastereoselectivities (89:11 dr).[16,17] The *N*-*tert*-butylsulfinyl group can prepare as not only an efficient chiral auxiliary for the asymmetric synthesis of ketamine, but also an amine protecting group.[18-20] Generally, the ketones with the electron-donating substituent on the aromatic ring could participate better in the reaction, resulting in the obtained products with better yields (75%–80%) and diastereoselectivities (>95 : 5 dr).[13-16] The sulfinyl group is eliminated from the Grignard addition product by treatment with HCl in protic solvents such as methanol to present

the amine salt in good yields.[13-20] Enantiomerically pure material may be provided by first chromatographing or recrystallizing the Grignard addition product prior to sulfinyl group removal or by either crystallizing the amine hydrochloride salt.[14-20] Amine (**6**) was obtained in the high isolated yield of 92%. The resulting chirality of the carbon center was proved again to be (*S*) by comparison of the optical rotation with the literature value.[21] In this procedure, for reach to (*S*)-ketamine further provides the nucleophilic addition upon *N*-sulfinyl cyclic imine where both conditions of ring and the sulfinyl group have the potential to control reaction diastereoselectivity.

2. Experimental

General

All the chemicals were used as purchased (Merck) for the reaction without further purification. All the organic solvents were purchased from commercial suppliers and were purified according to standard procedures. Lewis acids were also obtained from commercial suppliers. All reactions were carried out in oven-dried glassware under nitrogen atmosphere. Infrared spectra were recorded using a Perkin–Elmer Spectrom-100 FT-IR spectrometer. IR spectra of liquids were recorded as thin films on NaCl plates, and IR spectra of solids were recorded as KBr pellets. The ^{1}H NMR spectra were determined using TMS as an internal reference with an Avance FT NMR spectrometer operating at 250 MHz. The ^{13}C NMR spectra were determined using TMS as an internal reference with an Avance FT NMR spectrometer operating at 60 MHz. Mass spectra analyses were recorded on an Agilent Technologies, Model: 5975C VL MSD by EI mass spectrometry on a Q-TOF instrument. Preparative normal phase HPLC were performed on a

Waters HPLC prep 4000 system equipped with a 4000-controller pump by using column DAICEL CHIRALCEL OD-H; Detection: UV 254 nm, Mobile phases were 5% 2-propanol/*n*-hexane, Flow: 0.5 mL/min. Flash chromatography was performed using silica gel 60 (200–300 mesh). Thin layer chromatography was carried out on silica gel 60 F-254 TLC plates of 20 cm × 20 cm. Column chromatography was performed using Merck Silica gel 60 (0.063–0.200 mm). Elemental analysis on C, H and N were performed using a HN Heraeuse Elemental Analyser.

Synthesis of Intermediates:

2.1. Preparations of 2-(*N*-piperidin-1-methyl)cyclohexan-1-one (1):

Compound (**1**) was synthesized according to classical Mannich reaction, Mannich and Lammering, 1922.[22] A mixture of the cyclohexanone, paraformaldehyde, piperidine hydrochloride were heated under reflux in 20 mL acetic acid 95% v/v. Only for formation of piperidine hydrochloride, hydrochloric acid 37% v/v, 3 mL was added in to 10 mL piperidine. The mol ratios of cyclohexanone, paraformaldehyde, piperidine hydrochloride and duration of heating were as follows: 0.02, 0.01, 0.01, 2 h. The acetic acid was evaporated in vacuo to give compound **(1)** as solid crystals. After evaporation, compound was heated in 20 mL dry acetone under 45 °C at 30 min and were recrystalized from ethanol. The white crystals were dried in oven (mp. 101-105 °C). Then crystals were dissolved to water and on cooling were treated with sodium hydroxide 30% (pH=14) to give base. The mixture was extracted with ether. Finally, the mannich base, yellow liquid, was separated.

yellow liquid, (88%), Isolated yield = 0.078 g. IR (KBr): 2933, 2733, 1720, 1447, 1090, 1222, 865, 500 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 2.78 (dd, 1H, J= 12.75, 5.5), 2.51-2.70 (m, 1H), 2.25-2.48 (m, 5H), 2.15-2.25 (m, 2H), 2.00-2.15 (m, 1H), 1.80-2.00 (m, 1H), 1.70-1.81 (m,

2H), 1.47-1.65 (m, 4H), 1.20-1.51 (m, 2H) ppm.; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 211.3, 64.9, 57.5, 54.1, 47.7, 41.1, 32.1, 28.1, 25.0, 23.9, 23.6 ppm.; Mass spectrum (EI, 70 eV), *m*/*z* (*I*rel, %): $[M]^+$ 195 (13), 181 (8), 149 (8), 111 (13), 98 (10), 84 (8), 71 (13), 57 (100), 41 (51); Elemental analysis for $C_{12}H_{21}NO$: Calculated C 73.85, H 10.77, N 7.18, Found C 73.98, H 10.79, N 7.20%.

2.2. Preparations of (*S*)-2-methyl-*N*-((*E*)-2-(piperidine-1-methyl)cyclohexyliden)propane-2-sulfonamide (2):

A 0.5 M solution of $Ti(OEt)_4$ (11.72 g, 51.4 mmol) and ketone (**1**) (5.01 g, 25.7 mmol) in THF was prepared under a N_2 atmosphere. Then, (*S*)-*tert*-butanesulfunamine (3.11 g, 25.7 mmol) was added and the flask was heated. Conversion was followed by TLC, and the mixture cooled immediately upon completion. Once at room temperature, the mixture was poured into an equal volume of brine while rapidly stirring. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel where the organic layer was washed with brine. The brine layer was extracted once with a small volume of EtOAc, and the combined organic portions were dried (Na_2SO_4), filtered, and concentrated. The sulfinylimine (**2**) were purified either by flash chromatography.

red liquid (85%), Isolated yield = 0.101 g. IR (KBr): 3300, 2950, 2933, 2733, 1668, 1620, 1030, 800 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ: 2.76 (dd, 1H, J= 12.75, 5.5), 2.45-2.64 (m, 2H), 2.20-2.45 (m, 6H), 2.09-2.22 (m, 2H), 1.85-2.07 (m, 2H), 1.70-1.82(m, 2H), 1.57-1.69 (m, 2H), 1.42-1.57 (m, 3H), 1.27-1.42 (m, 2H), 1.15 (s, 9H) ppm.; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 168.5, 56.7, 53.6, 53.4, 47.0, 40.6, 32.0, 31.5, 27.0, 26.8, 24.2, 23.4, 23.2, 22.8, 20.9 ppm.; $[\alpha]_D^{20}$: +42 (*c* 1.2, $CHCl_3$) Mass spectrum (EI, 70 eV), *m*/*z* (*I*rel, %): $[M]^+$ 298 (10), 280 (4), 267 (5), 250 (3),

214 (13), 186 (20), 149 (20), 127 (20), 111 (30), 98 (65), 84 (37), 57 (100), 41 (40); Elemental analysis for $C_{16}H_{30}N_2SO$: Calculated C 64.42, H 10.06, N 9.39, Found C 64.45, H 10.12, N 9.43%.

2.3. Preparations of (*S*)-*N*-((1*R*)-1-(2-chlorophenyl)-2-(piperidin-1-methyl)cyclohexyl)-2-methylpropane-2-sulfinamide (3):

To a solution of containing 4.00 g (13.4 mmol) of product (**2**) in dry THF (25 mL) at −78 °C under N_2 was added dropwise a solution of 2-cholorophenylmagnesium bromid (8.60 g (40.2 mmol) in 50 mL ether) The mixture was stirred at −78 °C and then was warmed to room temperature with stirring overnight. The reaction mixture was quenched by the addition of saturated aqueous Na_2SO_4. The organic layer was removed, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The products obtained 3 were purified either by silica gel chromatography.

yellow liquid, (80%), Isolated yield = 0.104 g. IR (KBr): 3500, 3300, 3026, 2950, 2933, 2733, 1600, 1620, 1445, 1351, 1030, 984, 800, 780, 710, 500 cm^{-1}.; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 7.53-7.56 (m, 1H), 7.37-7.40 (m, 1H), 7.16-7.19 (m, 1H), 7.06-7.11 (m, 1H), 5.48-5.49 (NH), 2.88 (dd, 1H, J= 12.75, 5.5), 2.54-2.76 (m, 2H), 2.36-2.54 (m, 2H), 2.28-2.36 (m, 1H), 2.13-2.28 (m, 2H), 1.91-2.13 (m, 3H), 1.71-1.90 (m, 4H), 1.43-1.70 (m, 4H), 1.29 -1.43 (m, 2H), 1.19-1.29 (m, 2H), 1.16 (s, 9H) ppm.; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 133.0, 129.7, 128.0, 127.8, 127.3, 121.6, 66.1, 57.1, 54.0, 47.4, 46.1, 41.2, 32.6, 27.4, 24.5, 24.0, 22.9, 22.3, 21.5 ppm. $[\alpha]_D^{20}$: −53 (*c* 1.2, $CHCl_3$) Mass spectrum (EI, 70 eV), *m*/*z* (*I*rel, %): $[M]^+$ 410 (6), 377 (5), 363 (3), 341 (3), 326 (5), 289 (4), 238 (6), 180 (12), 139 (100), 120 (19), 111 (22), 105 (34), 69 (28), 55 (22);

Elemental analysis for $C_{22}H_{35}N_2SOCl$: Calculated C 64.39, H 8.53, N 6.83, Found C 64.56, H 8.71, N 6.91%.

2.4. Preparations of 1-(((2*R*)-2-(((*S*)-*tert*-butylsulfinyl)(methyl)amino)-2-(2-chlorophenyl) cyclohexyl)methyl)-1-methylpiperidin-1-ium (4):

2.00 g (4.9 mmol) of product (**3**) in 20 mL acetone was homogenized at room temperature. Then, K_2CO_3 (2.00 g (14.4 mmol)) was added and the flask was refluxed for 2 h. The solution was stirred, and methyl iodide (1.5 g (10.5 mmol)) was added dropwise over 30 min. After the addition was completed, the mixture was stirred for 1.5 h. The mixture was filtered and concentrated under reduced pressure. The oil obtained was extracted twice with 25 mL *n*-hexane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product obtained was purified either by silica gel chromatography.

yellow oil, (70%), Isolated yield = 0.129 g. IR (KBr): 3300, 2900, 2800, 2750, 1620, 1600, 1490, 1351, 1030, 984, 800, 780, 710, 500 cm^{-1}.; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 7.67-7.7 (m, 1H), 7.53-7.58 (m, 1H), 7.35-7.41 (m, 1H), 3.40 (s, 3H), 2.76 (dd, 1H, J= 12.75, 5.5), 2.44-2.64 (m, 2H), 2.17 (s, 3H), 2.07-2.15 (m, 2H), 1.96-2.07 (m, 2H), 1.51-1.96 (m, 12H), 1.37-1.53 (m, 2H), 1.24 (s, 9H) ppm.; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 133.7, 130.3, 128.3, 127.8, 122.3, 68.0, 67.2, 66.9, 63.0, 52.2, 38.6, 33.1, 30.2, 29.6, 28.8, 23.3, 22.8, 22.0, 20.3 ppm. $[\alpha]_D^{20}$: −64 (*c* 1.2, $CHCl_3$) Mass spectrum (EI, 70 eV), *m*/*z* (*I*rel, %): $[M]^+$ 439 (3), 424 (4), 410 (5), 393 (4), 377 (6), 341 (4), 326 (3), 305 (5), 205 (3), 139 (100), 111 (22), 105 (34), 69 (22), 55 (20); Elemental analysis for $C_{24}H_{40}N_2SOCl$: Calculated C 65.6, H 9.11, N 6.38, Found C 65.74, H 9.23, N 6.42%.

2.5. Preparations of (*S*)-*N*-((*R*)-1-(2-chlorophenyl)-2-methylenecyclohexyl)-*N*, 2-dimethylpropane-2-sulfinamide (5):

1.50 g (3.4 mmol) of quaternary salt (**4**) was dissolved in 25 mL mixture of water and methanol. The volume ratio was as follows: 1 to 9 respectively. Next, the $NaHCO_3$ (0.70 g (8.3 mmol)) was added and then was stirred for 15 min. Then solution was refluxed for 3h at 80 °C. The oil obtained was extracted twice with 25 mL *n*-hexane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product obtained was purified either by silica gel chromatography.

Yellow liquid, (90%). Isolated yield = 0.052 g. IR (KBr): 3350, 3100, 2900, 2820, 1620, 1600, 1406, 1175, 760, 680, 500 cm^{-1}.; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 7.68-7.70 (m, 1H), 7.53-7.58 (m, 1H) 7.36-7.41 (m, 1H), 4.84 (s, 1H), 4.78 (s, 1 H), 2.20-2.61 (m, 1H), 2.47 (m, 3H), 2.09 (s, 3H), 1.82-2.04 (m, 2H), 1.49-1.81 (m, 3H), 1.31-1.57 (m, 2H), 1.23 (s, 9H) ppm.; ^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 156.7, 130.0, 129.6, 129.2, 128.9, 127.7, 126.0, 107.9, 67.6, 56.3, 34.3, 31.3, 28.8, 29.1, 23.9, 22.9, 22.2 ppm. $[\alpha]_D^{20}$: −55 (c 1.2, $CHCl_3$) Mass spectrum (EI, 70 eV), *m*/*z* (*I*rel, %): $[M]^+$ 339 (7), 324 (4), 309 (3), 293 (15), 279 (9), 256 (6), 277 (9), 222 (27), 209 (12), 186 (24), 167 (30), 149 (100), 139 (45), 127 (30), 111 (45), 85 (76), 57 (67); Elemental analysis for $C_{18}H_{26}NSOCl$: Calculated C 49.20, H 5.92, N 3.19, Found C 49.63, H 6.03, N 3.32%.

2.6. Preparations of (*R*)-1-(2-chlorophenyl)-*N*-methyl-2-methylenecyclohexan-1-amine (6):

1.00 g (2.9 mmol) of alkene obtained (**5**) and MeOH (20 mL) were mixtured and aq HCl 36% (3.5 mL) was added. The reaction was stirred at 70 °C for 5 h, during which the cleavage was monitored by TLC. Volatiles were removed under reduced pressure. Then, reaction mixture was

cooled to 25 °C and was added 10 mL saturated aqueous Na_2SO_4. Next, the many drop NH_3 was added (to pH= 6). The amine obtained was extracted twice with 25 mL EtOAc and concentrated to pale liquid. The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave a residue, which was purified by flash chromatography to afford the corresponding amine.

Colorless liquid (80%), Isolated yield = 0.034 g. IR (KBr): 3500, 2750, 1920, 1700, 1600, 1406, 1195, 680 cm^{-1}.; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 7.16-7.52 (m, 4H), 4.86 (s, 1H), 4.61 (s, 1H), 3.27 (NH), 2.46-2.67 (m, 3H), 2.37 (s, 3H), 1.90-2.2 (m, 2H), 1.60-1.87 (m, 3H) ppm.; ^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 157.1, 132.8, 130.7, 129.9, 128.1, 127.2, 126.3, 108.2, 63.8, 40.8, 32.2, 29.8, 28.4, 18.0 ppm. $[\alpha]_D^{20}$: −49 (*c* 1.2, $CHCl_3$) Mass spectrum (EI, 70 eV), *m*/*z* (*I*rel, %): $[M]^+$ 235 (6), 220 (12), 206 (18), 193 (15), 175 (18), 164 (12), 152 (9), 140 (15), 124 (18), 111 (21), 98 (100), 94 (15), 84 (24), 67 (18), 55 (21), 41 (15); Elemental analysis for $C_{14}H_{18}NCl$: Calculated C 71.48, H 7.65, N 5.95, Found C 71.56, H 7.74, N 6.01%.

2.7. Preparations of (*S*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone ((*S*)-ketamine) (7):

Amine (**6**) (0.30 g (1.3 mmol)) was dissolved in 10% HCl solution (8 mL). Concentration under reduced pressure gave the corresponding amine HCl salt. Ozone was passed into a solution of the amine HCl salt in MeOH (20 mL) at −78 °C, terminating the ozonolysis upon observing the distinctive blue color of ozone. After purging with nitrogen, dimethyl sulfide (1600 μL) was added at −78 °C. The solution was allowed to warm up to room temperature and concentrated under reduced pressure to give the crude material, which was dissolved in EtOH (6 mL). When *n*-hexane was added, the HCl salt of (*S*)-ketamine was immediately crystallized. Finally, the salt

was again dissolved in a 10% NaOH solution (12 mL) and the corresponding amine was extracted with ether (30 mL). After evaporation of solvent, the amine was purified by flash chromatography (50% EtOAc/*n*-hexane) to afford (*S*)-ketamine. The enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OD-H column).

Colorless crystals; (75%), Isolated yield = 0.032 g. Mp 122 °C. IR (KBr): 2960, 2500, 2420, 1728, 1560, 1440, 1380, 1100, 960, 775, 700, 580 cm^{-1}.; ^{1}H NMR ($CDCl_3$) δ: 7.62-7.82 (1H, m), 7.41-7.62 (1H, m), 7.32-7.41 (1H, m), 7.21-7.32 (1H, m), 2.76–2.84 (1H, m), 2.44–2.55 (2H, m), 2.11 (3H, s), 2.06–2.15 (1H, m), 1.96–2.05 (1H, m), 1.82–1.90 (1H, m), 1.72–1.78 (3H, m) ppm.; ^{13}C NMR ($CDCl_3$) δ: 209.0, 137.5, 133.8, 131.2, 129.5, 128.8, 126.7, 70.2, 39.4, 38.6, 29.1, 28.1, 21.8 ppm.; Mp: 122 ^{o}C; $[\alpha]_D^{20}$: −43.2 (*c* 1.2, EtOH);[21] ee = 75% by HPLC analysis (DAICEL CHIRALCEL OD-H column). Mass spectrum (EI, 70 eV), *m*/*z* (*I*rel, %): $[M]^+$ 237 (12), 222 (27), 186 (23), 167 (29), 149 (100); Elemental analysis for $C_{13}H_{16}NOCl$: Calculated C 65.82, H 6.75, N 5.90, Found C 65.98, H 6.86, N 5.99%.

3. Results and Discussion

In the present study, we prepared 2-(*N*-piperidino methyl) cyclohexanone (**1**) by the reaction of cyclohexanone with formaldehyde and piperidine hydrochloride. In the classical Mannich procedures to β-aminoketones, yields are sometimes low because observed side reactions, such as deamination, occur under the reaction conditions. The rate of deamination should be inversely proportional to the basicity of the amine leaving group.[22,23] It was provided from the amine tertiary (**3**) by reaction with methyl iodide according to the procedure of Edwards et al.[24] On the other hand, the reaction condition was focused on the using of *N*-*tert*-butylsulfonamide with

Mannich base to afford sulfinylimine (**2**) in the presence of $Ti(OEt)_4$ with THF as solvent at 60 °C. The reaction emerged smoothly, giving the obtained sulfinyliminein 85% yield after 3 h (Table 1, entry 1). Also, in this investigation, some titanium-(IV) salts were searched, mainly to effect the condensation of sulfinamide with the ketone. Due to their Lewis acidity and excellent water-scavenging ability, Ti(IV) salts such as $Ti(OEt)_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ have been used to condense amines with ketones.[19] At experiments, $Ti(O\text{-}i\text{-}Pr)_4$ was moderately effective (Table 1, entries 5-7). Fortunately, $Ti(OEt)_4$ was found to be more efficient than $Ti(O\text{-}i\text{-}Pr)_4$ without promotion of the aldol condensation side reaction. An 85% yield was provided.

Based on prior studies on the synthesis of imines,[25,26] the thermal stability of the sulfinylketimine products appears to be correlated to the steric demand about the ketones that require more compelling conditions to condense deliver imine products that do not hydrolyze observably under these conditions. Although some *tert*-butanesulfinylimines decompose very slowly in air, they were stored dry at low temperatures (−4 °C) for extended periods of time. But, sulfinylimine (**2**) (derived from cyclohexanone) will fully hydrolyze over the course of 3 days in air. The relative stabilities of the *tert*-butanesulfinylimines to silica chromatography relate to the rates of hydrolysis in air. However, the sulfinylimine (**2**) not could be quickly chromatographed with *n*-hexane/Et_2O as eluent. Also, steric effects control the *E/Z* isomer ratios observed for sulfinylimines. The *E* isomer is only observed by NMR (250 MHz) in $CDCl_3$. Optimizing the reaction conditions was then carried out to ameliorate the yield of the reaction. The investigation of various solvents was shown in Table 1, and THF was found to be the best choice. The showing of the reaction time displayed that this transformation could complete in 3 h (entry 1), and extending reaction time resulted in a decrease in both yield (entries 3 and 7). Next, we evaluated Grignard reagent addition to *N*-sulfinylimine derived from Mannich base. In order,

optimizing the reaction conditions was then carried out to ameliorate both the yields and the diastereoselectivities of the reaction (Table 2).

The temperature was found to be important for this reaction. Elevating reaction temperature caused a significant improve in the yields (up to 90%), but brought dramatic decrease in diastereoselectivities (entries 3, 4). As shown in Scheme 3, a six-membered cyclic transition state with Mg coordinated to the oxygen of the sulfinyl group is consistent with the sense of induction.[26]

In this model, Grignard reagent ideally added to the imine from the less hindered face to afford (S_s , *R*) as major diastereomer (Scheme 3). Also, the proposed cyclic transition state is consistent with the reaction proceeding with highest selectivities in noncoordinating solvents. Notably, the best diastereoselectivity (95 : 5 dr) was obtained with CH_2Cl_2 as noncoordinating solvent, but along with really lower yield (65%, entry 6). The selectivity observed for Grignard reagent is also noteworthy, considering that transformation is performed in the coordinating solvent THF. Therefore, the best conditions for the Grignard reaction was obtained in THF as solvent (entry 1, Table 2). In this model, Grignard reagent ideally added to the imine from the less hampered face to afford (S_s , *S*) as major diastereomer (Scheme 3). The *N*-*tert*-butylsulfinyl group can present as not only an effective chiral auxiliary for the asymmetric synthesis of ketamine, but also an amine protecting group. The diastereoselectivity of the reaction should be determined by both equatorial attack upon the low-energy chair conformation and the stereochemistry of the sulfinyl group. However, the selectivity for additions to our cyclic imine should be dependent on the steric properties of the ring substituent located C2 and the aryl substituent. In this procedure, after three steps (methylation, deamination and deprotection), we was obtained the chiral

compound (**6**). Finally, by oxidation step was provided a nitrogen-substituted quaternary carbon bearing α-carbonyl group ((*S*)-ketamine).

4. Conclusions

In summary, the asymmetric synthesis of anesthetic (*S*)-ketamine was a very difficult challenge. We have presented a novel procedure for the synthesis of (*S*)-ketamine as antagonist of blocking the NMDA receptor. In this paper, we have proved a straightforward procedure for the construction of a chiral nitrogen-substituted carbon using an enantioselective 1,2-addition reaction of 2-cholorophenyl magnesium bromide to chiral α- *N*-sulfinylimine-Mannich base, 2, having α-chiral sulfinylimine auxiliary. We have confirmed that use of (*S*)-*tert*-butanesulfinamide is advantageous in strategy because the *tert*-butanesulfinyl group actuates the imine for nucleophilic addition and provides as a potent chiral directing group. We speculate that the diastereoselectivity of the reaction may be determined by both equatorial attack upon the low-energy chair conformation and the stereochemistry of the sulfinyl group. After deprotection, the approach served the chiral compound with a nitrogen-substituted quaternary carbon bearing α-carbonyl group. Thus, the asymmetric synthesis of (*S*)-ketamine, was accomplished with good selectivity (>75% ee).

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Table 1. Condensations of TBSA with compound (**1**) mediated by Ti(IV) compounds

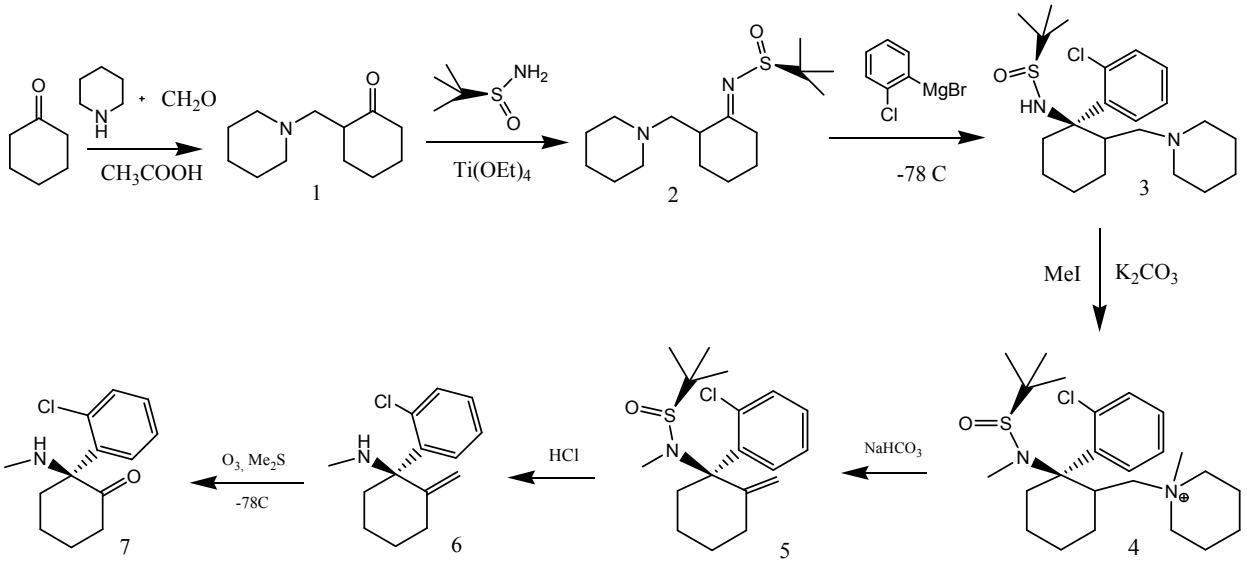
Entry	Lewis acid[a]	Solvent	Time (h)	Yield (%)[b]
1	$Ti(OEt)_4$	THF	3	85
2	$Ti(OEt)_4$	THF	12	85
3	$Ti(OEt)_4$	THF	24	70
4	$Ti(OEt)_4$	THF	3	75
5	$Ti(OEt)_4$	Toluene	3	65
6	$Ti(O\text{-}i\text{-}Pr)_4$	THF	12	65
7	$Ti(O\text{-}i\text{-}Pr)_4$	THF	24	60
8	$Ti(O\text{-}i\text{-}Pr)_4$	Toluene	3	60

a) Mol ratio of Lewis acid to monoketal, 2 to 1 b) Yield determined by NMR analysis.

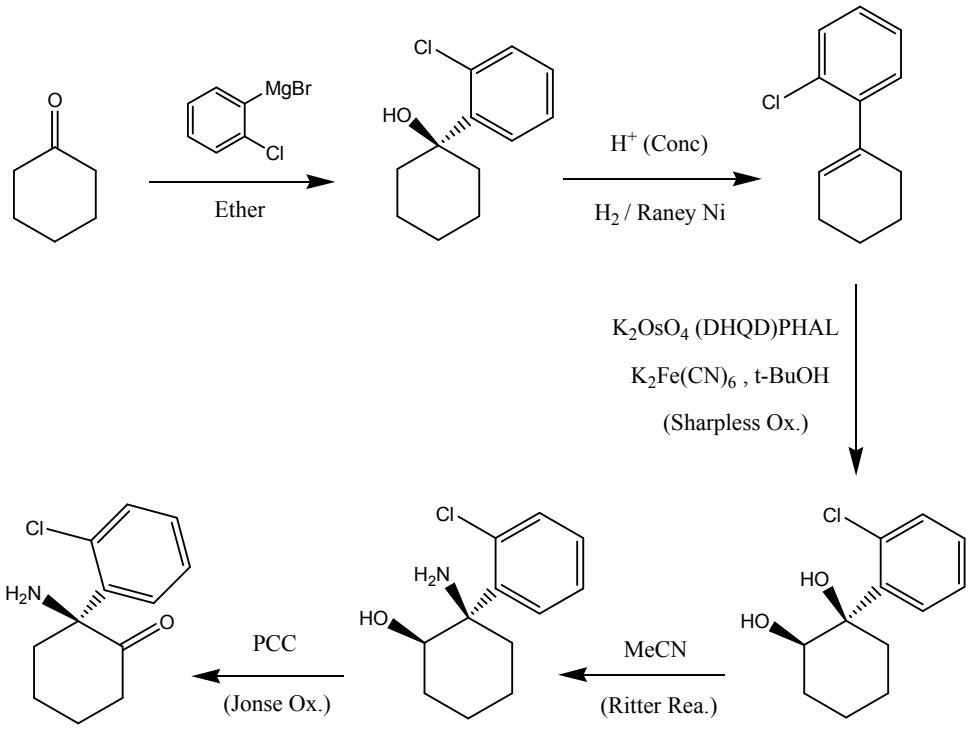
Table 2. Optimization of addition of Grignard reagent to *N-tert*-butanesulfinylimine (**2**)

Entry	Solvent	*T*/°C	Time (h)	Yield (%)[a]	dr (S: R) [b]
1	THF	−78	15	80	90:10
2	THF	−50	15	87	80:20
3	THF	0	15	90	75:25
4	THF	25	15	94	68:32
5	THF	−78	24	85	90:10
6	CH_2Cl_2	−78	24	65	95:5
7	Toluene	−78	15	67	80:20
8	Toluene	−78	24	67	73:27
9	Toluene	−50	15	75	70:30

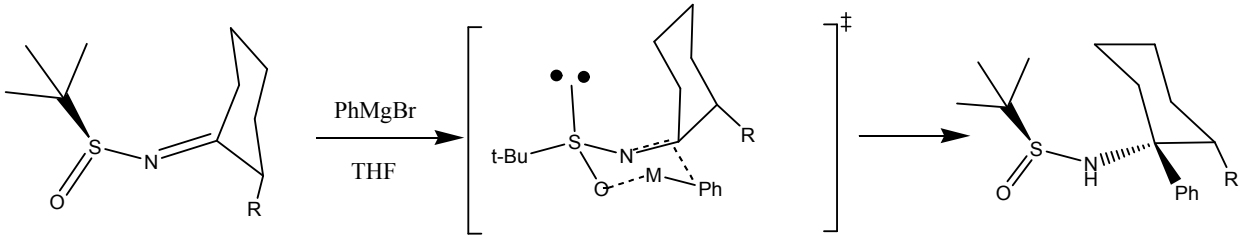
Isolated yield of diastereomerically and analytically pure material after chromatography. a) Yield determined by NMR analysis. b) Diastereomeric ratio was determined by chiral HPLC assay.



Scheme 1. Asymmetric synthesis of (*S*)-ketamine



Scheme 2. Asymmetric synthesis of (*S*)-norketamine



Scheme 3. Intermediates of nucleophilic addition to *N*-sulfinylimine