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A synthesis, including asymmetric synthesis, of α-quaternary α-amino aldehydes from ketones and chloromethyl *p*-tolyl sulfoxide via sulfinylaziridines

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Abstract—Treatment of 1-chlorovinyl *p*-tolyl sulfoxides, prepared from ketones and chloromethyl *p*-tolyl sulfoxide, with *N*-lithio arylamines resulted in the formation of sulfinylaziridines in good to high yields. The sulfinylaziridines were treated with *N*-lithio aniline or *N*-lithio *p*-chloroaniline to afford α-quaternary α-amino aldehydes in good yields. From α-quaternary α-amino aldehydes, α-quaternary α-amino acid esters and β-quaternary β-amino alcohols were obtained. When optically active chloromethyl *p*-tolyl sulfoxide was used in this procedure, a method for the synthesis of optically active α-quaternary α-amino aldehydes was realized. The reaction mechanism, including asymmetric induction, for the formation of the sulfinylaziridines is described.

1. Introduction

α-Amino aldehydes are obviously one of the most important compounds in organic chemistry and various investigations of their chemistry and synthesis have been reported.[1] α-Amino aldehydes are also very important intermediates for the synthesis of α-amino acids[2] and amino alcohols.[3] Recently, α-quaternary α-amino acids,[4] including cyclic α-quaternary α-amino acids,[5] have received considerable attention. On the other hand, as synthesis of compounds having a quaternary carbon is still a formidable task,[6] development of new methods for the construction of quaternary stereogenic center will contribute to synthetic organic chemistry.

We have been investigating development of new synthetic methods utilizing conjugate addition of nucleophiles to 1-chlorovinyl *p*-tolyl sulfoxides, which were easily prepared from carbonyl compounds with chloromethyl *p*-tolyl sulfoxide.[7] Recently, we investigated conjugate addition of *N*-lithio arylamines to 1-chlorovinyl *p*-tolyl sulfoxides **1** and found that the reaction gave sulfinylaziridines **2** or α-amino aldehydes **3** depending upon the amount of used *N*-lithio arylamines (Scheme 1).[8] In this paper, a new synthetic method for α-amino aldehydes **3** from cyclic- and acyclic ketones is described in detail. An asymmetric synthesis of α-amino aldehydes **3** by using optically active 1-chlorovinyl *p*-tolyl sulfoxides **1** and the reaction mechanism for the formation of sulfinylaziridines **2** are discussed.

2. Results and discussion

2.1. Treatment of 1-chlorovinyl *p*-tolyl sulfoxides with *N*-lithio arylamines

At first, 1-chlorovinyl *p*-tolyl sulfoxide **4** was synthesized from 1,4-cyclohexanedione mono ethylene ketal[9] and treated with 5 equiv of *N*-lithio aniline in THF at 0 °C to room temperature for 1 h. Starting material **4** disappeared and somewhat surprisingly, α-amino aldehyde **5** was found to be the product (Scheme 2). On the other hand, treatment of **4** with almost 1 equiv of *N*-lithio aniline at 0 °C resulted in the formation of sulfinylaziridine **6** in 92% yield with a trace of α-amino aldehyde **5**. Obviously, the α-amino aldehyde **5** was thought to be derived from **4** via the sulfinylaziridine **6**. In fact, treatment of **6** with excess *N*-lithio aniline in THF at room temperature gave α-amino aldehyde **5** in 94% yield.

It is worth noting that the product, sulfinylaziridine **6**, was obtained as a single isomer, though **6** has two stereogenic centers. This fact implied that an asymmetric synthesis of sulfinylaziridines and α-amino aldehydes could be possible by using unsymmetrical ketones and optically active chloromethyl *p*-tolyl sulfoxide. The asymmetric synthesis of the α-amino aldehydes and the reaction mechanism for the formation of sulfinylaziridines will be discussed later.

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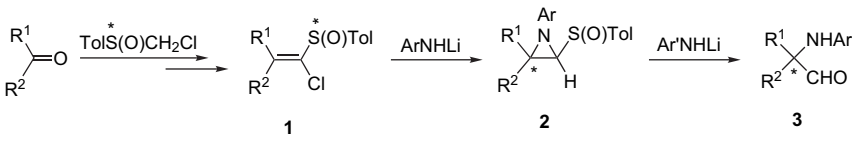
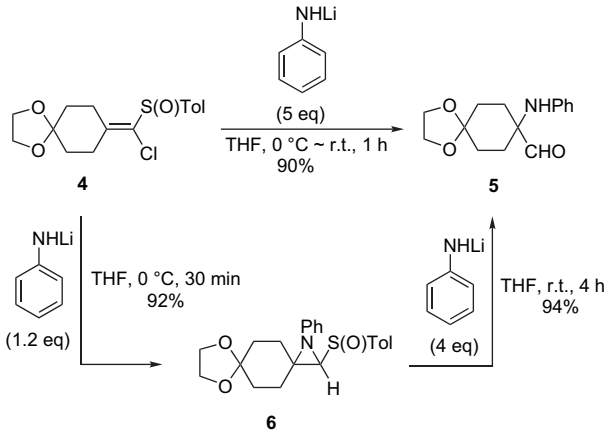
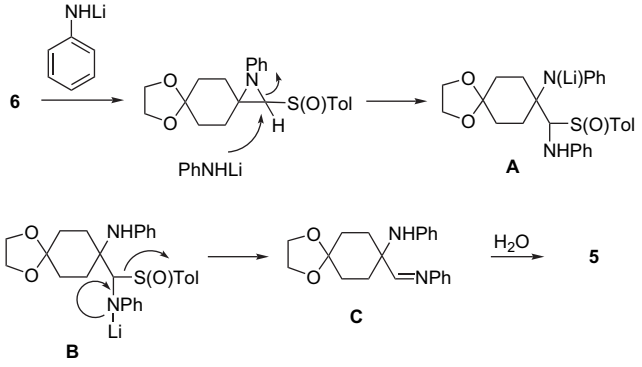


Scheme 1.



Scheme 2.

A plausible mechanism for the reaction of sulfinylaziridine **6** with *N*-lithio aniline to give α-amino aldehyde **5** is shown in Scheme 3. Thus, nucleophilic attack of *N*-lithio aniline to the carbon bearing the sulfinyl group results in the formation of the ring-opened adduct **A**. Intramolecular proton shift of **A** could give **B**, from which elimination of sulfenate takes place to afford an imine **C**. Hydrolysis of the imine group with water during the work-up affords α-amino aldehyde **5**.



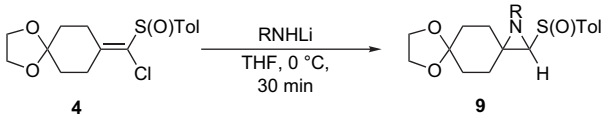
Scheme 3. A plausible mechanism for the reaction of sulfinylaziridine **6** with *N*-lithio aniline to give α-amino aldehyde **5**.

As mentioned above, α-amino aldehydes are very important compounds in organic chemistry and we planned to investigate a direct synthesis of α-amino aldehydes from 1-chlorovinyl *p*-tolyl sulfoxides (Scheme 4). Thus, 1-chlorovinyl *p*-tolyl sulfoxide **4** was treated with excess *N*-lithio *p*-chloroaniline at room temperature for 1 h. As expected, this reaction gave the desired α-amino aldehyde **7a**; however, the yield was not satisfactory. When this reaction was carried out with *N*-lithio *p*-anisidine, a mixture of α-amino aldehyde **7b** and imine **8b** was obtained. Unfortunately, these products were hardly separated by chromatography. We concluded that this method was beyond hope for direct synthesis of α-amino aldehydes **3** from 1-chlorovinyl *p*-tolyl sulfoxides **1**.

Next, we investigated the generality of the reaction of **4** with *N*-lithio amines to give sulfinylaziridines **9** and the results are summarized in Table 1. As shown in the table, *o*-anisidine, *p*-anisidine, *p*-chloroaniline, and *p*-cyanoaniline gave 84–93% yields of the desired sulfinylaziridines (**9a**–**9d**); however, *p*-nitroaniline gave no reaction (entry 5). Interestingly, the reaction of **4** with *N*-lithio alkylamines (benzylamine and hexylamine) resulted in decomposition of **4**. Obviously, basicity of the *N*-lithio amines plays a critical role in these reactions.

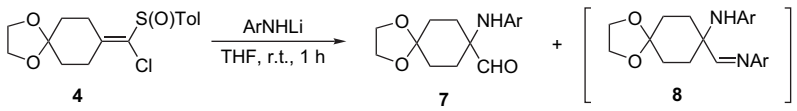
As referred above, treatment of sulfinylaziridine **6** with *N*-lithio aniline gave α-amino aldehyde **5** in high yield (see

Table 1. Treatment of 1-chlorovinyl *p*-tolyl sulfoxide **4** with *N*-lithio arylamines and *N*-lithio alkylamines



Entry	RNHLi		9	
	R	Equiv		Yield (%)
1	*o*-$MeOC_6H_4$	2.1	**9a**	90
2	*p*-$MeOC_6H_4$	1.3	**9b**	90
3	*p*-ClC_6H_4	1.7	**9c**	93
4	*p*-CNC_6H_4	2.3	**9d**	84
5	*p*-$NO_2C_6H_4$	1.7		0[a]
6	$PhCH_2$	2.2		0[b]
7	$CH_3(CH_2)_5$	5.2		0[b]

[a] No reaction was observed.
[b] A complex mixture was obtained.

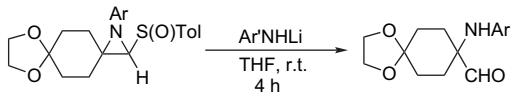


Ar = *p*-ClC_4H_6 (8 eq) **7a** (66%)
Ar = *p*-$CH_3OC_4H_6$ (8 eq) **7b** + **8b** (82%; **7b**:**8b**=1:1)

Scheme 4. Treatment of 1-chlorovinyl *p*-tolyl sulfoxide **4** with excess *N*-lithio *p*-chloroaniline and *N*-lithio *p*-anisidine.

Scheme 2). In order to obtain α-amino aldehydes from the sulfinylaziridines (**9a**–**9d**), the reaction of these sulfinylaziridines with *N*-lithio aniline or *N*-lithio *p*-chloroaniline was investigated and the results are summarized in Table 2. Thus, sulfinylaziridine **9a** was added to a solution of *N*-lithio aniline in THF and the reaction mixture was stirred for 4 h to afford the desired α-amino aldehyde bearing an *o*-methoxyphenyl group on the nitrogen **7c** in 90% yield without any imine (entry 1). As shown in entries 2 and 3, sulfinylaziridine **9b** reacted with both *N*-lithio aniline and *N*-lithio *p*-chloroaniline to give α-amino aldehyde **7b** in up to 91% yield. The reaction of **9c** with *N*-lithio *p*-chloroaniline gave the desired α-amino aldehyde **7a** in 90% yield. However, the reaction of sulfinylaziridine **9d** with *N*-lithio aniline did not proceed and using further excess of *N*-lithio aniline resulted in the decomposition of **9d**. As a whole, α-amino aldehydes **7c** and **7b** were synthesized from **4** through the sulfinylaziridines (**9a** and **9b**) in 72 and 68% overall yields, respectively.

Table 2. Treatment of sulfinylaziridines **9** with *N*-lithio arylamines



9 **7**

Entry	9		Ar′NHLi		7	
		Ar	Ar′	Equiv		Yield (%)
1	**9a**	*o*-$MeOC_6H_4$	C_6H_5	5.5	**7c**	90
2	**9b**	*p*-$MeOC_6H_4$	C_6H_5	4.0	**7b**	76
3	**9b**	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	5.5	**7b**	91
4	**9c**	*p*-ClC_6H_4	*p*-ClC_6H_4	4.5	**7a**	90
5	**9d**	*p*-CNC_6H_4	C_6H_5	8.5		—[a]

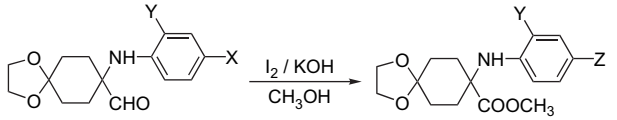
[a] A complex mixture was obtained.

2.2. Oxidation of the α-amino aldehydes to α-amino acid methyl esters with iodine in the presence of KOH in methanol

As mentioned above, α-quaternary α-amino acids are quite interesting compounds and various kinds of synthetic methods have been reported.[4] In order to extend the above-mentioned reactions to a new synthetic method for the synthesis of α-quaternary α-amino acid derivatives, oxidation of the aldehyde group to carboxylic esters was examined. Because a highly oxidizable arylamine moiety is present in the α-amino aldehydes (**5**, **7a**, **7b**, and **7c**), a very mild oxidizing agent must be selected for the oxidation of the aldehyde group. After some fruitless investigation, we tried a very classic oxidation of aldehydes to esters with iodine in methanol[10] and the results are summarized in Table 3.

At first, according to the procedure reported by Inch et al.,[10a] a solution of potassium hydroxide in methanol was added dropwise to a solution of aldehyde **5** and iodine in methanol at 40 °C and the reaction mixture was stirred for 10 min (entry 1). The starting material disappeared and a methyl ester was obtained; however, the aromatic ring was iodinated at the *para*-position. The α-amino aldehyde having *p*-chlorophenyl group **7a** gave good yield of the desired methyl ester **10b** (entry 2). The α-amino aldehyde having *p*-methoxyphenyl group **7b** gave the desired methyl ester **10c**; however, the yield was only 26% (entry 3). The α-amino aldehyde having *o*-methoxyphenyl group **7c** gave the desired methyl ester **10d**; however, again the *para*-position of the aromatic ring was iodinated (entry 4).

Table 3. Oxidation of the α-amino aldehydes with iodine in methanol in the presence of KOH



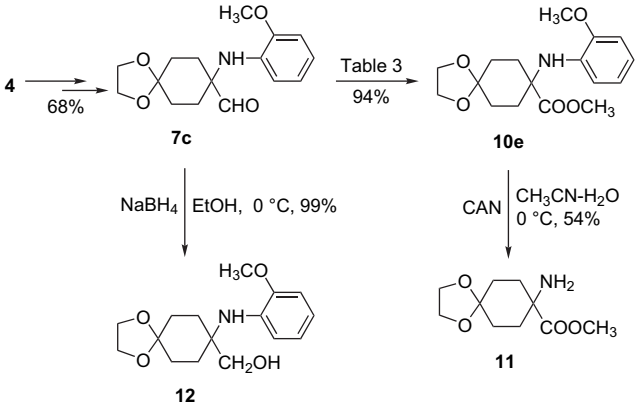
10

Entry	α-Amino aldehyde			I_2 (equiv)	Temp (°C)	10		
		X	Y				Z	Yield (%)
1	**5**	H	H	3.8[a]	40	**10a**	I	70
2	**7a**	Cl	H	2.6[a]	rt	**10b**	Cl	89
3	**7b**	OCH_3	H	1.2[a]	rt	**10c**	OCH_3	26
4	**7c**	H	OCH_3	3.0[a]	rt	**10d**	I	65
5	**7c**	H	OCH_3	3.0[b]	rt	**10e**	H	94

[a] A solution of KOH in methanol was added to a solution of the α-amino aldehyde and iodine in methanol.

[b] A solution of iodine and KOH in methanol was stirred at room temperature for 10 min and then a solution of the α-amino aldehyde in methanol was added to the reaction mixture.

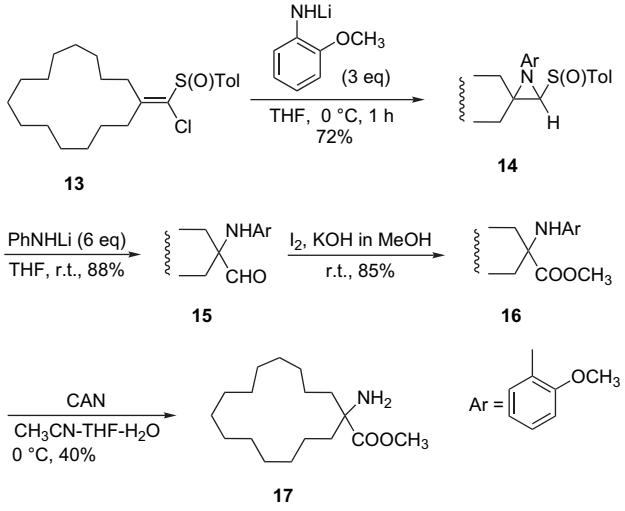
These reaction conditions were further modified and finally quite good conditions were found, which are as follows. Thus, at first, a solution of iodine (3 equiv) and KOH in methanol was stirred at room temperature for 10 min. To this solution was added a solution of the aldehyde **7c** in methanol and the reaction mixture was stirred at room temperature for 10 min. Gratifyingly, this reaction gave the desired methyl ester **10e** in 94% yield (entry 5). Finally, the *o*-methoxyphenyl group of **10e** was removed by treatment with ceric ammonium nitrate (CAN)[11] to give cyclic α-quaternary α-amino acid methyl ester **11** in 54% yield (Scheme 5). Reduction of the aldehyde group of **7c** was easily conducted with $NaBH_4$ in ethanol to give β-quaternary β-amino alcohol **12** in a quantitative yield.



Scheme 5. A synthesis of cyclic α-quaternary α-amino acid methyl ester **11** and β-quaternary amino alcohol **12** from α-amino aldehyde **7c**.

In order to investigate the generality of this procedure for the synthesis of α-quaternary α-amino aldehyde, it was carried out starting from 1-chlorovinyl *p*-tolyl sulfoxide **13**, which was easily synthesized from cyclopentadecanone [9] (Scheme 6). Treatment of **13** with 3 equiv of *N*-lithio *o*-anisidine at

0 °C for 1 h gave sulfinylaziridine **14** as a single product in 72% yield. Opening of the aziridine ring was found to be rather sluggish; however, using 6 equiv of *N*-lithio aniline resulted in smooth formation of the desired α-amino aldehyde **15** in high yield. The oxidation of the aldehyde group was carried out in the procedure described above to give methyl ester **16** in good yield. Finally, removal of the *o*-methoxyphenyl group was successful with CAN to give cyclic α-quaternary α-amino acid methyl ester having a large ring **17**; however, the yield was again not satisfactory.



Scheme 6. A synthesis of cyclic α-quaternary α-amino acid methyl ester **17** from 1-chlorovinyl *p*-tolyl sulfoxide **13** derived from cyclopentadecanone.

2.3. An asymmetric synthesis of α-quaternary α-amino aldehyde starting from unsymmetrical ketones and (*R*)-chloromethyl *p*-tolyl sulfoxide and the reaction mechanism for the formation of the sulfinylaziridines

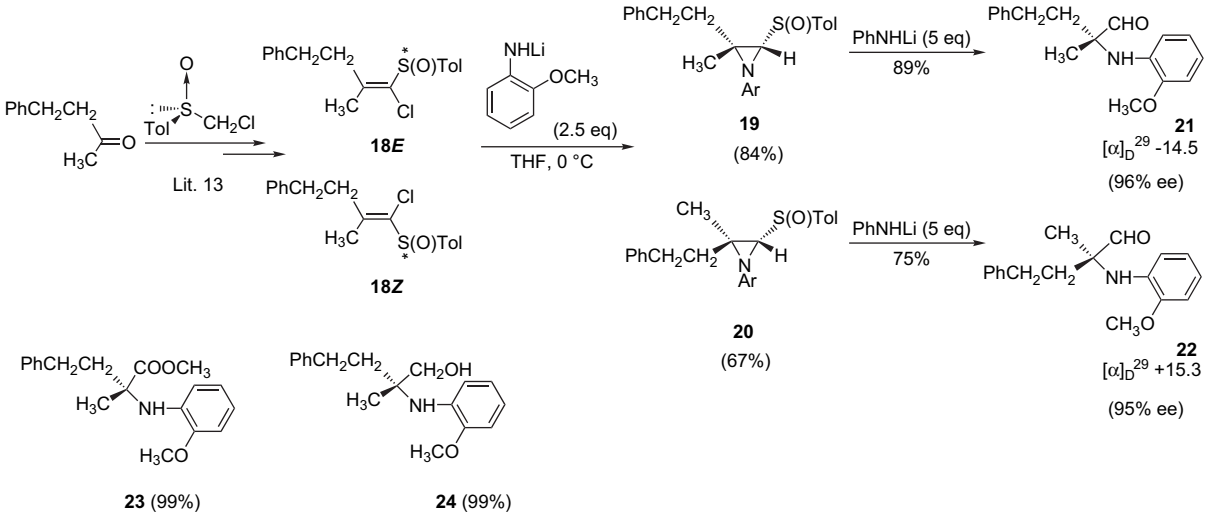
As already described, the reaction of 1-chlorovinyl *p*-tolyl sulfoxide **4** with *N*-lithio aniline resulted in the formation of a single isomer of sulfinylaziridine **6** (see Scheme 2). Based on this result we studied an asymmetric synthesis of α-quaternary α-amino aldehydes from unsymmetrical ketones with optically active chloromethyl *p*-tolyl sulfoxide (Scheme 7).

At first, 1-chlorovinyl *p*-tolyl sulfoxides **18***E* and **18***Z* were synthesized from 4-phenyl-2-butanone and optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide[12] in high overall yield.[13] Vinylsulfoxides **18***E* and **18***Z* were treated with *N*-lithio *o*-anisidine at 0 °C to give sulfinylaziridines **19** and **20**, respectively, as single isomer, which was judged from their ^{1}H NMR. Relative stereochemistry of both methyl and sulfinyl groups of **19** and **20** was easily determined from the chemical shift of the methyl groups. Thus, the chemical shift of the methyl hydrogens of **20** (δ 1.72) was markedly lowered compared with those of **19** (δ 1.06), which indicated that the methyl carbon and the sulfinyl group of **20** should be cis.[14]

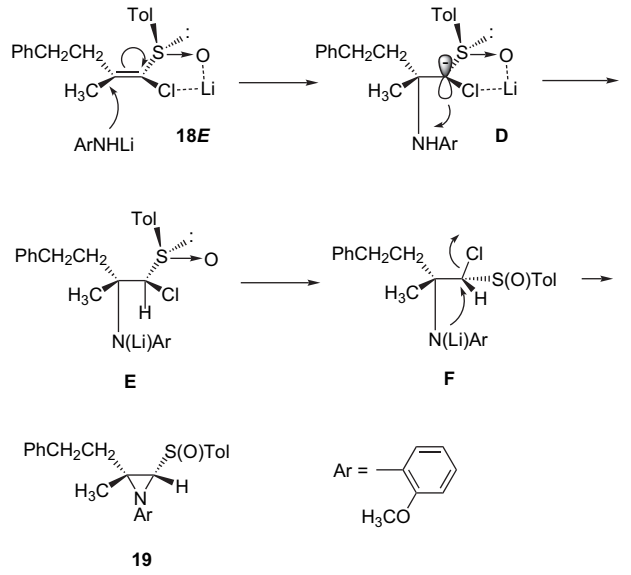
Both sulfinylaziridines **19** and **20** were treated with *N*-lithio aniline at room temperature to afford the desired α-amino aldehydes **21** and **22**, respectively, in good yields. IR and ^{1}H NMR spectra of **21** and **22** were superimposable; however, the sign of their specific rotation was reverse, which indicated that **21** and **22** are enantiomers to each other. The enantiomeric excess (ee) of **21** and **22** was determined to be 96 and 95%, respectively, by HPLC using a chiral stationary column (CHIRALCEL-OD). The absolute configuration of the aldehydes **21** and **22** was determined to be as shown in Scheme 7 by the synthesis of **21** using the already established method reported by us.[12,14]

As the absolute configuration of the carbon bearing the methyl group of **21** was determined to be *R*, the whole stereochemistry of sulfinylaziridine **19** was determined also as shown in Scheme 7. With the whole structure of sulfinylaziridine **19** in hand, the reaction mechanism and chiral induction of the reaction of **18***E* with *N*-lithio aniline can now be proposed as shown in Scheme 8.

Thus, in the reaction of **18***E* with *N*-lithio *o*-anisidine, the lithium cation forms a five-membered chelate between the oxygen of the sulfoxide and chlorine atom.[15] The nitrogen nucleophile would attack from the less hindered *re*-face to give **D**. Intramolecular proton transfer from the nitrogen to



Scheme 7.



Scheme 8.

the anionic carbon then takes place to give the intermediate **E**. Rotation of the carbon–carbon bond at 60° to afford a conformer **F**, in which the nitrogen attacks the carbon bearing a chlorine atom results in the formation of the optically active sulfinylaziridine **19**. From optically active α-amino aldehyde **21**, optically active α-quaternary α-amino acid methyl ester **23** and optically active β-amino alcohol **24** were obtained in quantitative yields.

In conclusion, a synthetic method for α-quaternary α-amino aldehydes from ketones through sulfinylaziridines was realized. Asymmetric synthesis of α-quaternary α-amino aldehydes and α-amino acid methyl esters was also developed by using optically active chloromethyl *p*-tolyl sulfoxide as a starting material. The reaction mechanism of the reaction of 1-chlorovinyl *p*-tolyl sulfoxides with *N*-lithio arylamines could be proposed.

3. Experimental

3.1. General

Melting points were measured with a Yanaco MP-S3 micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 300, 500 and BRUKER UltraShield 300, 400 spectrometers. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. IR spectra were recorded on a Perkin–Elmer spectrum One FTIR instrument. Silica gel 60N (KANTO CHEMICAL) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent and reagent, THF was distilled from sodium diphenyl ketyl; aniline, 4-aminobenzonitrile, *p*-chloroaniline, *o*-anisidine, and *p*-anisidine were purified by Kugelrohr distillation.

3.1.1. 4,4-Ethylenedioxy-1-(*N*-phenylamino)cyclohexanecarbaldehyde (5). *n*-BuLi (1.6 M solution in hexane, 0.31 mL, 0.49 mmol) was added to a solution of aniline (0.053 mL, 0.58 mmol) in 1 mL of dry THF at 0 °C with stirring. The reaction mixture was stirred for 10 min. A solution of **4** (31.7 mg, 0.097 mmol) in 0.5 mL of THF was added to the reaction mixture. The temperature of the reaction mixture was allowed to warm to room temperature for 1 h. The reaction was quenched by satd aq NH_4Cl. The whole was extracted with AcOEt and the organic layer was washed once with satd aq NH_4Cl. The organic layer was dried over $MgSO_4$. The product was isolated by silica gel column chromatography to give **5** (23 mg; 90%) as colorless crystals; mp 99–100 °C (AcOEt–hexane); IR (KBr): 3392 (NH), 1711 (CO), 1600, 1091 cm^{-1}; ^{1}H NMR: δ 1.69–1.77 (4H, m), 1.94–1.99 (2H, m), 2.04–2.09 (2H, m), 3.90 (1H, br s, NH), 3.95 (4H, s), 6.57 (2H, d, J=5 Hz), 6.76 (1H, t, J=7.3 Hz), 7.14 (2H, t, J=7.3 Hz), 9.65 (1H, s). MS *m*/*z* (%): 261 (M$^+$, 6), 232 (100), 170 (32), 147 (7). Calcd for $C_{15}H_{19}NO_3$: M, 261.1364. Found *m*/*z*: 261.1367. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.96; H, 7.32; N, 5.45.

3.1.2. 6,6-Ethylenedioxy-1-phenyl-2-(*p*-tolylsulfinyl)-1-azaspiro[2.5]octane (6). *n*-BuLi (1.6 M solution in hexane, 2.06 mL, 3.24 mmol) was added to a solution of aniline (0.344 mL, 3.78 mmol) in 12 mL of dry THF at 0 °C with stirring. The reaction mixture was stirred for 10 min. A solution of **4** (882.5 mg, 2.7 mmol) in 8 mL of THF was added to the reaction mixture and stirred for 30 min. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed once with satd aq NH_4Cl and dried over $MgSO_4$. The product was isolated by silica gel column chromatography to give **6** (953 mg, 92%) as colorless crystals; mp 151–154 °C (AcOEt–hexane); IR (KBr): 2946, 1595, 1492, 1398, 1048, 1030 (SO) cm^{-1}; ^{1}H NMR: δ 1.09–1.14 (1H, m), 1.38–1.43 (1H, m), 1.58–1.80 (3H, m), 1.95–2.00 (1H, m), 2.17–2.32 (2H, m), 2.45 (3H, s), 3.27 (1H, s), 3.91–4.00 (4H, m), 6.89 (2H, d, J=8.3 Hz), 6.99 (1H, t, J=7.4 Hz), 7.19 (2H, t, J=7.9 Hz), 7.39 (2H, d, J=8.0 Hz), 7.69 (2H, d, J=8.3 Hz). MS *m*/*z* (%): 383 (M$^+$, trace), 367 (44), 244 (39), 158 (100), 99 (29). Calcd for $C_{22}H_{25}NO_3S$: M, 383.1555. Found *m*/*z*: 383.1545. Anal. Calcd for $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.57; N, 3.65; S, 8.36. Found: C, 68.97; H, 6.39; N, 3.52; S, 8.39.

3.1.3. 4,4-Ethylenedioxy-1-[*N*-(4-chlorophenyl)amino]-cyclohexanecarbaldehyde (7a). Colorless crystals; mp 96.5–97.5 °C (AcOEt–hexane); IR (KBr): 3400 (NH), 2957, 1728 (CO), 1496, 1108, 819 cm^{-1}; ^{1}H NMR: δ 1.70–1.73 (4H, m), 1.91–1.95 (2H, m), 1.98–2.08 (2H, m), 3.95 (4H, s), 3.96 (1H, br s, NH), 6.49 (2H, d, J=8.9 Hz), 7.08 (2H, d, J=8.9 Hz), 9.59 (1H, s). MS *m*/*z* (%): 295 (M$^+$, 11), 266 (100), 204 (13), 169 (16). Calcd for $C_{15}H_{18}ClNO_3$: M, 295.0973. Found *m*/*z*: 295.0971. Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.60; H, 5.87; N, 4.82.

3.1.4. 4,4-Ethylenedioxy-1-[*N*-(4-methoxyphenyl)amino]-cyclohexanecarbaldehyde (7b). Colorless crystals; mp 82–83 °C (AcOEt–hexane); IR (KBr): 3377 (NH), 2948, 1709 (CO), 1521, 1237, 1038 cm^{-1}; ^{1}H NMR: δ 1.67–1.77 (4H, m), 1.87–1.91 (2H, m), 1.99–2.05 (2H, m), 3.59 (1H, br s, NH), 3.73 (3H, s), 3.95 (4H, s), 6.57 (2H, d, J=8.9 Hz), 6.73 (2H, d, J=8.9 Hz), 9.64 (1H, s). MS *m*/*z* (%): 291 (M$^+$, 12), 262 (100), 200 (18), 177 (7). Calcd for

$C_{16}H_{21}NO_4$: M, 291.1469. Found *m/z*: 291.1472. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.60; H, 7.19; N, 4.74.

3.1.5. 4,4-Ethylenedioxy-1-[*N*-(2-methoxyphenyl)amino]-cyclohexanecarbaldehyde (7c). Colorless crystals; mp 101.5–102.5 °C (AcOEt–hexane); IR (KBr): 3430 (NH), 1722 (CO), 1514, 1255, 1085, 756 cm^{-1}; ^1H NMR: δ 1.68–1.77 (4H, m), 1.99–2.07 (4H, m), 3.86 (3H, s), 3.95 (4H, s), 4.64 (1H, s, NH), 6.45 (1H, d, J=7.6 Hz), 6.70–6.80 (3H, m), 9.65 (1H, s). MS *m/z* (%): 291 (M^+, 10), 262 (100), 200 (19). Calcd for $C_{16}H_{21}NO_4$: M, 291.1469. Found *m/z*: 291.1486. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.94; H, 7.19; N, 4.80.

3.1.6. Imine (8b). Colorless oil; IR (neat): 3391 (NH), 2952, 2834, 1651, 1514, 1504, 1246, 1106, 1035, 826 cm^{-1}; ^1H NMR: δ 1.74–1.84 (4H, m), 1.99–2.06 (2H, m), 2.15–2.22 (2H, m), 3.72, 3.79 (each 3H, s), 3.96 (4H, s), 6.71 (4H, s), 6.86, 7.03 (each 2H, d, J=8.8 Hz), 7.84 (1H, s). MS *m/z* (%): 396 (M^+, 28), 262 (100), 256 (21). Calcd for $C_{23}H_{28}N_2O_4$: M, 396.2049. Found *m/z*: 396.2047.

3.1.7. 6,6-Ethylenedioxy-1-(2-methoxyphenyl)-2-(*p*-tolylsulfinyl)-1-azaspiro[2.5]octane (9a). Colorless crystals; mp 161–162 °C (AcOEt–hexane); IR (KBr): 2953, 1501, 1444, 1120, 1035 (SO), 764 cm^{-1}; ^1H NMR: δ 1.14–1.19 (1H, m), 1.26–1.32 (1H, m), 1.53–1.65 (3H, m), 2.05–2.17 (2H, m), 2.36–2.42 (1H, m), 2.45 (3H, s), 3.30 (1H, s), 3.87 (3H, s), 3.88–3.99 (4H, m), 6.77–6.86 (3H, m), 6.96–7.01 (1H, m), 7.39 (2H, d, J=8.0 Hz), 7.71 (2H, d, J=8.0 Hz). MS *m/z* (%): 413 (M^+, trace), 397 (27), 274 (38), 188 (100), 99 (18). Calcd for $C_{23}H_{27}NO_4S$: M, 413.1661. Found *m/z*: 413.1662. Anal. Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39; S, 7.75. Found: C, 66.37; H, 6.49; N, 3.43; S, 7.75.

3.1.8. 6,6-Ethylenedioxy-1-(4-methoxyphenyl)-2-(*p*-tolylsulfinyl)-1-azaspiro[2.5]octane (9b). Colorless amorphous; IR (KBr): 3452, 2950, 1507, 1241, 1086, 1035 (SO) cm^{-1}; ^1H NMR: δ 1.14–1.20 (1H, m), 1.37–1.44 (1H, m), 1.51–1.58 (1H, m), 1.69–1.77 (2H, m), 1.94–2.01 (1H, m), 2.14–2.29 (2H, m), 2.45 (3H, s), 3.23 (1H, s), 3.74 (3H, s), 3.91–4.00 (4H, m), 6.73 (2H, d, J=9.0 Hz), 6.83 (2H, d, J=9.0 Hz), 7.39 (2H, d, J=8.0 Hz), 7.68 (2H, d, J=8.0 Hz). MS *m/z* (%): 413 (M^+, trace), 274 (45), 188 (100), 186 (63). Calcd for $C_{23}H_{27}O_4NS$: M, 413.1661. Found *m/z*: 413.1668.

3.1.9. 6,6-Ethylenedioxy-1-(4-chlorophenyl)-2-(*p*-tolylsulfinyl)-1-azaspiro[2.5]octane (9c). Colorless crystals; mp 144–146 °C (AcOEt–hexane); IR (KBr): 2951, 1491, 1400, 1091, 1049 (SO), 836 cm^{-1}; ^1H NMR: δ 1.07–1.11 (1H, m), 1.41–1.44 (1H, m), 1.62–1.73 (3H, m), 1.93–1.97 (1H, m), 2.20–2.27 (2H, m), 2.45 (3H, s), 3.20 (1H, s), 3.93–3.99 (4H, m), 6.80 (2H, d, J=8.5 Hz), 7.14 (2H, d, J=8.5 Hz), 7.40 (2H, d, J=8.0 Hz), 7.68 (2H, d, J=8.0 Hz). MS *m/z* (%): 417 (M^+, trace), 278 (45), 192 (100), 99 (44). Calcd for $C_{22}H_{24}ClNO_3S$: M, 417.1166. Found *m/z*: 417.1165. Anal. Calcd for $C_{22}H_{24}ClNO_3S$: C, 63.22; H, 5.79; N, 3.35; S, 7.67; Cl, 8.48. Found: C, 62.86; H, 5.64; N, 3.35; S, 7.62; Cl, 8.61.

3.1.10. 6,6-Ethylenedioxy-1-(4-cyanophenyl)-2-(*p*-tolylsulfinyl)-1-azaspiro[2.5]octane (9d). Colorless crystals; mp 194.5–195 °C (CH_2Cl_2–hexane); IR (KBr): 2963, 2223 (CN), 1603, 1505, 1088, 1047 (SO), 853 cm^{-1}; ^1H NMR: δ 1.55–1.60 (1H, m), 1.80–1.83 (2H, m), 1.86–2.40 (5H, m), 2.46 (3H, s), 3.26 (1H, s), 3.96–4.03 (4H, m), 6.24 (2H, d, J=8.0 Hz), 7.31 (2H, d, J=8.0 Hz), 7.36 (2H, d, J=8.0 Hz), 7.67 (2H, d, J=8.0 Hz). MS *m/z* (%): 409 (M^+, 14), 269 (100), 183 (46), 154 (36). Calcd for $C_{23}H_{24}N_2O_3S$: M, 409.1586. Found *m/z*: 409.1590. Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.29; H, 5.70; N, 6.89.

3.1.11. Methyl[1-(4-iodophenyl)amino-4,4-ethylenedioxycyclohexyl]carboxylate (10a). A 4% solution of potassium hydroxide in methanol was added dropwise to a solution of aldehyde **5** (100 mg, 0.383 mmol) and iodine (186 mg, 1.45 mmol) in methanol at 40 °C until the color of the reaction mixture diminished. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed once with satd aq NH_4Cl and dried over $MgSO_4$. The product was isolated by silica gel flash column chromatography to give **10a** (113 mg; 70%) as colorless crystals; mp 121–123 °C (AcOEt–hexane); IR (KBr): 3390 (NH), 1729 (CO), 1591, 1504, 1242, 1107 cm^{-1}; ^1H NMR: δ 1.65–1.82 (4H, m), 2.05–2.09 (2H, m), 2.19–2.27 (2H, m), 3.68 (3H, s), 3.95 (5H, s, OCH_2-CH_2O, NH), 6.36 (2H, d, J=7.0 Hz), 7.39 (2H, d, J=7.0 Hz). MS *m/z* (%): 417 (M^+, 29), 358 (100), 231 (7), 169 (22). Calcd for $C_{16}H_{20}INO_4$: M, 417.0437. Found *m/z*: 417.0432.

3.1.12. Methyl [1-(4-chlorophenyl)amino-4,4-ethylenedioxycyclohexyl]carboxylate (10b). Colorless crystals; mp 111–114 °C (AcOEt–hexane); IR (KBr): 3408 (NH), 2951, 1731 (CO), 1493, 1107, 756 cm^{-1}; ^1H NMR: δ 1.66–1.69 (2H, m), 1.70–1.83 (2H, m), 2.05–2.10 (2H, m), 2.19–2.25 (2H, m), 3.68 (3H, s), 3.90 (1H, br s, NH), 3.95 (4H, s), 6.51 (2H, d, J=9.0 Hz), 7.09 (2H, d, J=9.0 Hz). MS *m/z* (%): 325 (M^+, 14), 266 (100), 204 (13), 169 (13). Calcd for $C_{16}H_{20}ClNO_4$: M, 325.1080. Found *m/z*: 325.1081. Anal. Calcd for $C_{16}H_{20}ClNO_4$: C, 58.99; H, 6.19; N, 4.30; Cl, 10.88. Found: C, 58.83; H, 6.07; N, 4.22; Cl, 10.92.

3.1.13. Methyl [1-(4-methoxyphenyl)amino-4,4-ethylenedioxycyclohexyl]carboxylate (10c). Colorless oil; IR (neat): 3392 (NH), 2951, 1729 (CO), 1509, 1242, 1107, 1036 cm^{-1}; ^1H NMR: δ 1.61–2.22 (8H, m), 3.67 (3H, s), 3.74 (3H, s), 3.90 (1H, br s, NH), 3.95 (4H, s), 6.64 (2H, d, J=6.8 Hz), 6.74 (2H, d, J=6.8 Hz). MS *m/z* (%): 321 (M^+, 27), 262 (100), 200 (23). Calcd for $C_{17}H_{23}NO_5$: M, 321.1575. Found *m/z*: 321.1585.

3.1.14. Methyl [1-(4-iodo-2-methoxyphenyl)amino-4,4-ethylenedioxycyclohexyl]carboxylate (10d). Colorless oil; IR (neat): 3428 (NH), 1732 (CO), 1513, 1224, 1110 cm^{-1}; ^1H NMR: δ 1.65–1.83 (4H, m), 2.10–2.31 (4H, m), 3.68 (3H, s), 3.82 (3H, s), 3.95 (4H, s), 6.44 (1H, d, J=6.6 Hz), 6.67 (1H, t, J=8.0 Hz), 6.76 (1H, t, J=7.0 Hz). MS *m/z* (%): 447 (M^+, 34), 388 (100), 262 (35). Calcd for $C_{17}H_{22}INO_5$: M, 447.0542. Found *m/z*: 447.0534.

3.1.15. Methyl [1-(2-methoxyphenyl)amino-4,4-ethylenedioxycyclohexyl]carboxylate (10e). A solution of I_2 (558 mg, 2.2 mmol) and potassium hydroxide (271 mg, 4.83 mmol) in methanol (10 mL) was stirred at room

temperature for 10 min and then aldehyde **7c** (200 mg, 0.686 mmol) in 2 mL of methanol was added. The reaction mixture was stirred at room temperature for 10 min. The reaction was quenched by adding satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed once with satd aq NH_4Cl and dried over $MgSO_4$. The product was isolated by silica gel flash column chromatography to give **10e** (206.7 mg, 94%) as a colorless oil; IR (neat): 3428 (NH), 2952, 1732 (CO), 1590, 1515, 1100, 1031 cm^{-1}; ^1H NMR: δ 1.64–1.70 (2H, m), 1.75–1.83 (2H, m), 2.13–2.28 (4H, m), 3.69 (3H, s), 3.84 (3H, s), 3.95 (4H, s), 4.64 (1H, br s, NH), 6.44 (1H, d, J=7.6 Hz), 6.68 (1H, t, J=7.6 Hz), 6.77 (2H, t, J=7.6 Hz). MS *m/z* (%): 321 (M^+, 22), 262 (100), 200 (16). Calcd for $C_{17}H_{23}NO_5$: M, 321.1575. Found *m/z*: 321.1587.

3.1.16. Methyl [1-amino-4,4-ethylenedioxycyclohexyl]-carboxylate (11). A solution of CAN (377 mg, 0.653 mmol) in 3 mL of water was added to a solution of **10e** (42 mg, 0.131 mmol) in 4 mL of CH_3CN at 0 °C with stirring. The reaction mixture was stirred at 0 °C for 30 min and then the solution was neutralized with 5% aq $NaHCO_3$. Na_2SO_3 (49.5 mg, 0.392 mmol) was added to the reaction mixture with stirring and after 10 min, the solution was diluted with satd aq $NaHCO_3$. The whole was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. The product was purified by silica gel column chromatography to give **11** (15 mg, 53%) as a colorless oil. Spectral data are reported in Ref. 14.

3.1.17. 1-[(4,4-Ethylenedioxy)-1-(4-methoxyphenylamino)-cyclohexyl]methanol (12). A solution of $NaBH_4$ (9 mg, 0.24 mmol) in 3 mL of ethanol was added to a solution of **7c** (50 mg, 0.172 mmol) in 4 mL of ethanol at 0 °C with stirring. The reaction mixture was stirred at 0 °C for 10 min and the reaction was quenched by powdered NH_4Cl. The whole was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. The product was purified by silica gel column chromatography to give **12** (50 mg, 99%) as colorless crystals; mp 73.5–74.5 °C (AcOEt–hexane); IR (KBr): 3427, 3398 (NH, OH), 2940, 1509, 1246, 1097, 1030, 744 cm^{-1}; ^1H NMR: δ 1.57–1.66 (4H, m), 1.72–1.78 (2H, m), 2.02–2.05 (2H, m), 2.62 (1H, br s, OH), 3.54 (2H, d, J=4.9 Hz), 3.87 (3H, s), 3.75 (4H, s), 4.09 (1H, br s, NH), 6.82–6.87 (4H, m). MS *m/z* (%): 293 (M^+, 12), 262 (100), 200 (18), 148 (7). Calcd for $C_{16}H_{23}NO_4$: M, 293.1626. Found *m/z*: 293.1629. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.66; H, 7.90; N, 4.75.

3.1.18. 1-(2-Methoxyphenyl)-2-(*p*-tolylsulfinyl)-1-aza-spiro[2.14]heptadecane (14). Colorless oil; IR (neat): 2928, 2856, 1593, 1499, 1456, 1045 (SO), 753 cm^{-1}; ^1H NMR: δ 0.41–0.45 (1H, m), 0.72–0.76 (1H, m), 0.92–1.93 (26H, m), 2.44 (3H, s), 3.16 (1H, s), 3.82 (3H, s), 6.81 (1H, d, J=8.0 Hz), 6.86 (1H, t, J=7.6 Hz), 6.98 (1H, t, J=8.0 Hz), 7.04 (1H, d, J=8.0 Hz), 7.38 (2H, d, J=7.9 Hz), 7.67 (2H, d, J=7.9 Hz). MS *m/z* (%): 481 (M^+, trace), 342 (100), 162 (7), 123 (9). Calcd for $C_{30}H_{43}O_2NS$: M, 481.3014. Found *m/z*: 481.3005.

3.1.19. 1-[*N*-(2-Methoxyphenyl)amino]cyclopentadecane-carbaldehyde (15). Colorless crystals; mp 110–111.5 °C ($CHCl_3$–CH_3OH); IR (KBr): 3419, 2928, 2856, 1727 (CO), 1600, 1509, 1456, 1222, 1030, 733 cm^{-1}; ^1H NMR: δ 1.14–1.36 (24H, m), 1.69–1.75 (2H, m), 1.79–1.85 (2H, m), 3.87 (3H, s), 4.44 (1H, s), 6.41 (1H, d, J=7.7 Hz), 6.67 (1H, t, J=7.7 Hz), 6.73 (1H, t, J=7.8 Hz), 6.75 (1H, d, J=7.6 Hz), 9.56 (1H, s). MS *m/z* (%): 359 (M^+, 17), 330 (100), 162 (28), 149 (14). Calcd for $C_{23}H_{37}NO_2$: M, 359.2824. Found *m/z*: 359.2833. Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.50; H, 10.33; N, 3.91.

3.1.20. 1-(2-Methoxyphenylamino)cyclopentadecane-carboxylic acid methyl ester (16). Colorless crystals; mp 101–102 °C ($CHCl_3$–CH_3OH); IR (KBr): 3415, 2929, 2858, 1729 (CO), 1602, 1514, 1225 cm^{-1}; ^1H NMR: δ 1.15–1.35 (24H, m), 1.80–1.86 (2H, m), 1.97–2.03 (2H, m), 3.68 (3H, s), 3.84 (3H, s), 4.46 (1H, s), 6.39 (1H, d, J=8.0 Hz), 6.65 (1H, t, J=7.9 Hz), 6.75 (2H, t, J=8.0 Hz). MS *m/z* (%): 389 (M^+, 12), 330 (100). Calcd for $C_{24}H_{39}O_3N$: M, 389.2930. Found *m/z*: 389.2923.

3.1.21. 1-Aminocyclopentadecanecarboxylic acid methyl ester (17). Spectral data are reported in Ref. 14.

3.1.22. (*R*)-(*E*)-1-Chloro-2-methyl-4-phenyl-1-(*p*-tolylsulfinyl)-1-butane (18*E*). Colorless crystals; mp 64–65 °C (hexane); IR (KBr): 3031, 2934, 1594, 1492, 1455, 1080, 1054 (SO), 814, 702 cm^{-1}; ^1H NMR: δ 2.07 (3H, s), 2.39 (3H, s), 2.85–2.91 (1H, m), 2.94–3.01 (2H, m), 3.15–3.21 (1H, m), 7.08–7.38 (9H, m). Anal. Calcd for $C_{18}H_{19}ClOS$: C, 67.80; H, 6.01. Found: C, 67.73; H, 5.89. $[\alpha]_D^{27}$ +244.4 (*c* 1.0, acetone; 99% ee).

3.1.23. (*R*)-(*Z*)-1-Chloro-2-methyl-4-phenyl-1-(*p*-tolylsulfinyl)-1-butane (18*Z*). Colorless crystals; mp 56–57 °C (hexane); IR (KBr): 3029, 2924, 1601, 1494, 1454, 1087, 1055 (SO), 889, 808 cm^{-1}; ^1H NMR: δ 2.25 (3H, s), 2.42 (3H, s), 2.56–2.61 (1H, m), 2.70–2.86 (3H, m), 7.31–7.40 (9H, m). Anal. Calcd for $C_{18}H_{19}ClOS$: C, 67.80; H, 6.01. Found: C, 67.62; H, 5.75. $[\alpha]_D^{27}$ +127.3 (*c* 1.0, acetone; 99% ee).

3.1.24. (*Z*)-1-(2-Methoxyphenyl)-2-methyl-2-(2-phenylethyl)-3-(*p*-tolylsulfinyl)aziridine (19). Colorless crystals; mp 101.5–103.5 °C (AcOEt–hexane); IR (KBr): 2999, 1594, 1498, 1456, 1250, 1219, 1035 (SO), 753 cm^{-1}; ^1H NMR: δ 1.06 (3H, s), 2.19 (1H, dt, J=12.8, 4.9 Hz), 2.34 (1H, dt, J=13.1, 4.9 Hz), 2.43 (3H, s), 2.83 (1H, dt, J=12.8, 4.9 Hz), 3.17 (1H, dt, J=13.1, 4.9 Hz), 3.20 (1H, s), 3.84 (3H, s), 6.83–7.01 (4H, m), 7.22–7.36 (7H, m), 7.63 (2H, d, J=8.3 Hz). Anal Calcd for $C_{25}H_{27}NO_2S$: C, 74.04; H, 6.71; N, 3.45. Found: C, 74.00; H, 6.63; N, 3.43.

3.1.25. (*E*)-1-(2-Methoxyphenyl)-2-methyl-2-(2-phenylethyl)-3-(*p*-tolylsulfinyl)aziridine (20). Colorless crystals; mp 162–163.5 °C (AcOEt–hexane); IR (KBr): 2929, 1593, 1496, 1456, 1045 (SO), 748 cm^{-1}; ^1H NMR: δ 0.992–0.98 (1H, m), 1.72 (3H, s), 1.80–1.86 (1H, m), 1.93–1.99 (1H, m), 2.44 (3H, s), 2.45–2.51 (1H, m), 3.15 (1H, s), 3.83 (3H, s), 6.78–7.97 (6H, m), 7.09–7.18 (3H, m), 7.39 (2H, d, J=8.0 Hz), 7.66 (2H, d, J=8.0 Hz). Anal Calcd for $C_{25}H_{27}NO_2S$: C, 74.04; H, 6.71; N, 3.45. Found: C, 73.98; H, 6.65; N, 3.46.

3.1.26. (*R*)-2-[*N*-(2-Methoxyphenyl)amino]-2-methyl-4-phenylbutanal (21). Colorless oil; IR (neat): 3400, 2938, 1732 (CO), 1603, 1509, 1457, 1223, 1029 (SO), 742 cm^{-1}; ^1H NMR: δ 1.44 (3H, s), 2.10–2.21 (2H, m), 2.48–2.63 (2H, m), 3.86 (3H, s), 4.80 (1H, s, NH), 6.52 (1H, dd, J= 7.7, 1.6 Hz), 6.72–6.81 (3H, m), 7.08 (2H, d, J=8.2 Hz), 7.16–7.26 (3H, m), 9.60 (1H, s). MS *m*/*z* (%): 283 (M^+, 7), 254 (100), 150 (18), 148 (16), 91 (31). Calcd for $C_{18}H_{21}NO_2$: M, 283.1571. Found *m*/*z*: 283.1576. $[\alpha]_D^{29}$ −14.5 (*c* 3.77, acetone; 96% ee).

3.1.27. (*S*)-2-[*N*-(2-Methoxyphenyl)amino]-2-methyl-4-phenylbutanal (22). Colorless oil. $[\alpha]_D^{29}$ +15.3 (*c* 2.48, acetone; 95% ee).

3.1.28. (*R*)-2-(2-Methoxyphenylamino)-2-methyl-4-phenylbutyric acid methyl ester (23). Colorless oil; IR (neat): 3412 (NH), 2951, 1733 (CO), 1603, 1516, 1456, 1224, 1030, 741 cm^{-1}; ^1H NMR: δ 1.63 (3H, s), 2.23–2.33 (2H, m), 2.50–2.68 (2H, m), 3.71 (3H, s), 3.85 (3H, s), 4.87 (1H, s, NH), 6.51–6.55 (1H, m), 6.67–6.82 (3H, m), 7.10–7.28 (5H, m). MS *m*/*z* (%): 313 (M^+, 21), 254 (100), 208 (15), 148 (24), 91 (28). Calcd for $C_{19}H_{23}NO_3$: M, 313.1676. Found *m*/*z*: 313.1671. $[\alpha]_D^{25}$ −7.0 (*c* 0.77, acetone; 95% ee).

3.1.29. (*R*)-2-(2-Methoxyphenylamino)-2-methyl-4-phenyl-1-butanol (24). Colorless oil; IR (neat): 3400 (NH, OH), 2939, 1601, 1509, 1459, 1221, 1030, 753 cm^{-1}; ^1H NMR: δ 1.33 (3H, s), 1.72–1.82 (1H, m), 1.94–2.05 (1H, m), 2.49 (1H, br s), 2.55–2.72 (2H, m), 3.48 (1H, d, J=11.0 Hz), 3.67 (1H, d, J=11.0 Hz), 3.86 (3H, s), 6.81–6.93 (4H, m), 7.06–7.26 (5H, m). MS *m*/*z* (%): 285 (M^+, 9), 254 (100), 180 (9), 148 (11), 91 (24). Calcd for $C_{18}H_{23}NO_2$: M, 285.1728. Found *m*/*z*: 285.1729. $[\alpha]_D^{26}$ −9.8 (*c* 1.0, acetone; 95% ee).

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