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EPIMERIZATION OF *TRANS*-3-ARYLAZIRIDINE- 2-CARBOXYLATES AT THE C3 POSITION †

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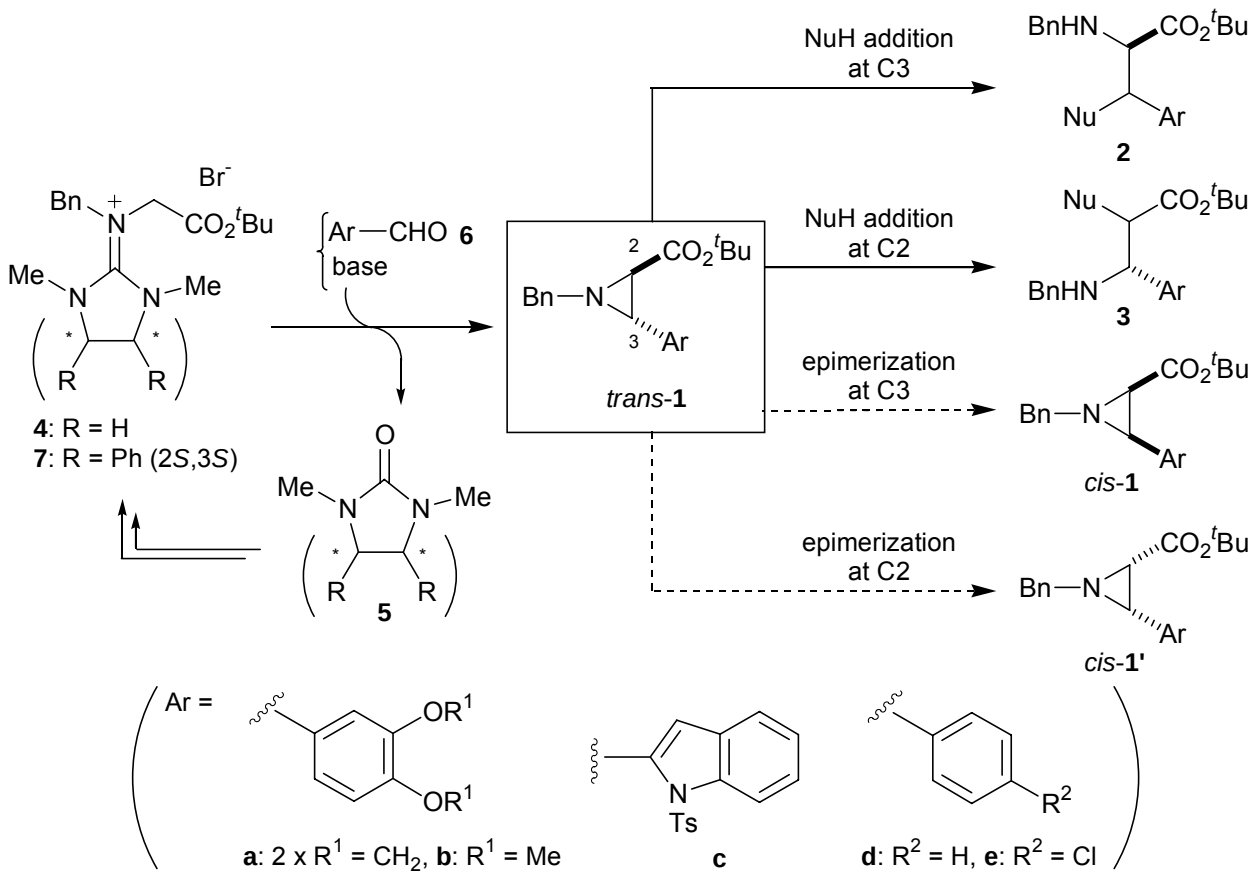
Abstract – We describe here effective epimerization of *trans* to *cis* isomer of 1-benzyl-3-arylaziridine-2-carboxylates. The combination of samarium metal, iodine and *N*,*N*-dimethylaminoethanol promoted the epimerization of *trans* isomer to a *ca.* 1 : 1 mixture of *cis* and *trans* ones. Investigating more effective catalyst, indium chloride was found to afford a *ca.* 2 : 1 mixture of *cis* and *trans* isomers. Epimerization at benzylic position in the aziridines is suggested from the result with optically active ones. Preparation of *cis*-2-indolylaziridine towards construction of aziridinomitosene skeleton was achieved in this epimerization reaction.

INTRODUCTION

Aziridines are one of the versatile synthetic intermediates for the preparation of *N*-containing biologically active compounds.[1,2] Among them, synthesis and utilization of aziridine-2-carboxylates **1** are much focused because they are convertible to α- **2** or β-amino acid derivatives **3** by regioselective ring-opening reactions at C3-N and C2-N bond, respectively (Scheme 1).[1,3,4] We have reported an atom-economical synthesis of 3-arylaziridine-2-carboxylates **1** from guanidinium salt **4** (derived from ureas **5**) and aromatic aldehydes **6** mediated by a base such as 1,1,3,3-tetramethylguanidine (TMG).[5] Synthesis of optically active **1** was also achieved with employing chiral guanidinium salt **7** in high ee. In this process, *trans* isomers mainly formed when electron-rich aromatic aldehydes such as piperonal and *p*-anisaldehyde were used and were successfully applied to the synthesis of β-aminoalcohols.[6,7] However, corresponding *cis*-aziridines, applicable to the synthesis of natural products containing *cis*-aziridines such as mitomycin C,[8] were minor products in this process, whereas the ratio of *cis* isomer was increased up to 3 : 1 when aromatic aldehydes with non-substituted or electron-withdrawing group are used.[9] Epimerization of



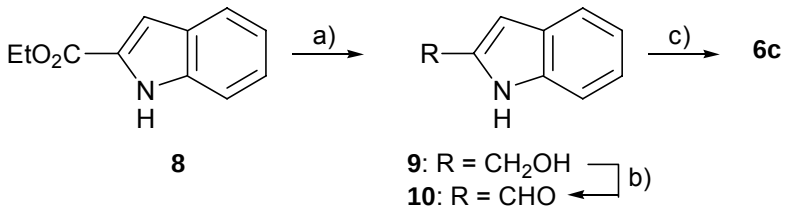
Scheme 1 Synthesis of 3-arylaziridine-2-carboxylates *trans*-**1** from guanidinium salts **4** or **7** and aromatic aldehydes **6** and their transformations

trans-aziridines is one of the candidates for preparation of the corresponding *cis* isomers. During our trials for reductive ring opening of *trans*-3-arylaziridine-2-carboxylates to amino acid derivatives, we observed the epimerization of *trans* isomer to *cis* one. We describe here the new method for the synthesis of *cis*-aziridinecarboxylates *cis*-**1** by epimerization of the corresponding *trans* isomer *trans*-**1** and its application for the synthesis of *cis*-indolylaziridine derivative, the useful synthetic intermediate for the construction of aziridinomitosene skeleton.[10]

RESULTS

Synthesis of Aziridines

The *trans* isomers of aziridine substrates *trans*-**1** employed in this study were synthesized according to the reported procedure from guanidinium salt **4** or chiral one **7** and aldehydes **6** (Scheme 1).[5,8] The *N*-tosylindole-2-carboxyaldehyde (**6c**), the substrate for the synthesis of indolylaziridine **1c**, was prepared through $LiAlH_4$ reduction and MnO_2 oxidation of commercially available indole-2-carboxylate **8** followed by tosylation (Scheme 2).



Scheme 2 Synthesis of *N*-tosylindole-2-carboxylaldehyde (**6c**) Conditions: a) $LiAlH_4$, THF, 0 °C, 30 min; b) MnO_2, CH_2Cl_2, rt, 14 h (77%, 2 steps); c) TsCl, NaH, DMF, 0 °C, 2 h (61%).

Trials for regioselective ring opening of *trans*-1a

Aziridines (**11** in Figure 1) are classified into two groups, "activated" and "unactivated" (or nonactivated) aziridines, dependent on their substituents on the nitrogen atom,[1,3] in which the former category includes electron-withdrawing substituents such as tosyl, *tert*-butoxycarbonyl or acyl functions, whereas a hydrogen atom and alkyl substituents are typical for the latter one. Although the reactivity of "activated" aziridines were well investigated, there are only limited reports on the utilization of "unactivated" aziridines for organic synthesis.[6,11] For example, β-aminoester synthesis via regioselective reductive ring opening of aziridinecarboxylates by the reductions with magnesium metal in methanol and with samarium (II) iodide (SmI_2)[12] had been reported. In the former condition, only "activated" aziridines **12** gave the corresponding β-aminoester **13**.[13] On the other hand, the latter SmI_2 afforded the corresponding β-aminoesters **13** and **15** from "activated" **12**[14] and even from "unactivated" 2-acylaziridine **14** (R = H in Figure 1),[15] respectively, in the presence of *N*,*N*-dimethylaminoethanol

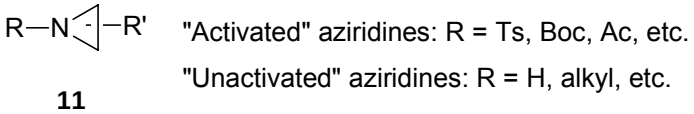
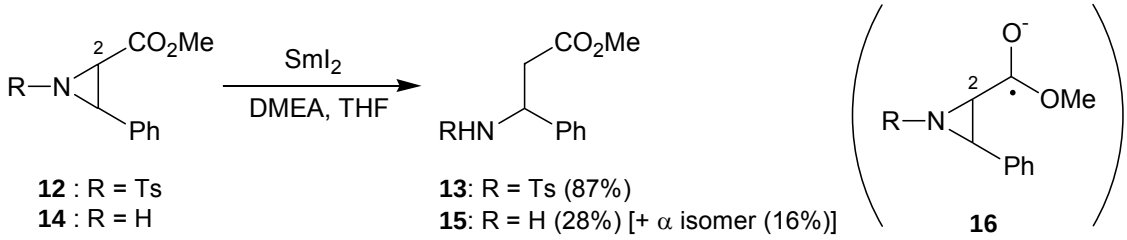


Figure 1 "Activated" and "unactivated" aziridines

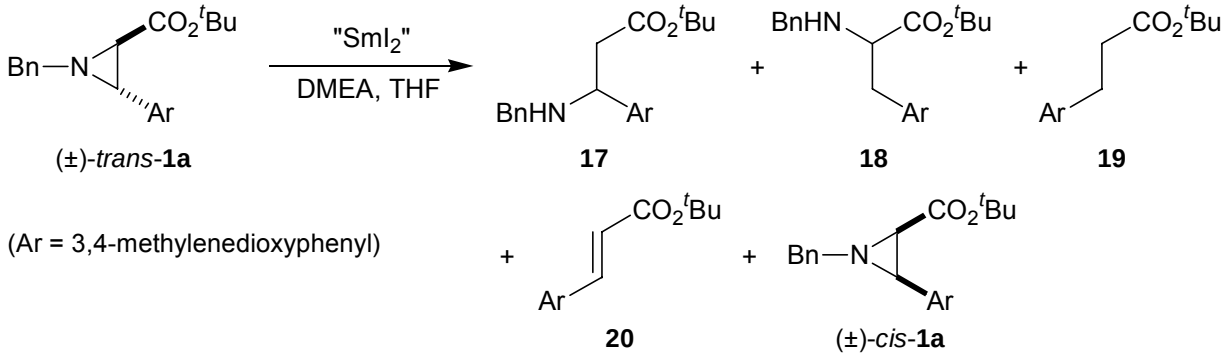


Scheme 3 Reported synthesis of β-aminoesters **13** and **15** via reductive ring-opening of "activated" **12** and "unactivated" aziridines **14** by SmI_2/DMEA system

(DMEA) as a proton source and a Lewis acid scavenger (Scheme 3). The selective formation of β-aminoesters **13** and **15** could be explained by the regioselective C2-N bond cleavage of ketyl radicals **16**.

Thus, we attempted reductive ring opening of "unactivated" aziridinecarboxylate (±)-*trans*-**1a** (R = benzyl in Figure 1) with SmI_2 for the synthesis of β-aminoester **17**. However, most of the starting material was recovered and only small amount of desired β-aminoester **17** was obtained on the reaction with SmI_2, prepared from samarium metal (Sm) and diiodomethane (CH_2I_2), in the presence of DMEA at -78 °C (run 1, Table 1). The reaction was sluggish even at -40 °C to give α- **18** and β-aminoesters **17** in low yields (run 2). Therefore, we turned to utilize molecular iodine (I_2) for the activation of Sm.[16] This reaction system has the following advantages towards conventional Sm/CH_2I_2 system for the preparation of SmI_2: 1) Sm has higher reductive potential compared to SmI_2 (Sm^{2+}/Sm = -2.68 V, Sm^{3+}/Sm^{2+} = -1.55 V);[17] 2) iodide anion could be reusable in Sm(0)-Sm(II) and Sm(II)-Sm(III) conversions. Two procedures for the preparation of SmI_2 from Sm and I_2 reported by Yanada *et al.* were

Table 1 Trials for ring-opening reaction of aziridine (±)-*trans*-**1a** with "SmI_2"

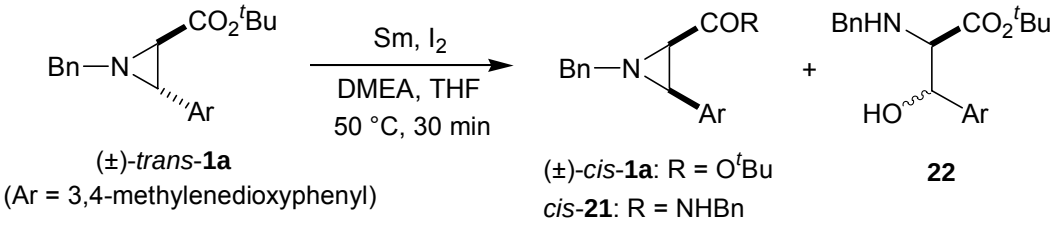


run	method	I_2 (eq)	conditions	crude (%)	product ratio [a]					
					trans-**1a**	**17**	**18**	**19**	**20**	*cis*-**1a**
1 [b]	-	-	-78 °C, 30 min	57	88	12	-	-	-	-
2 [b]	-	-	-40 °C, 30 min	77	70	8	22	-	-	-
3	A	0.4	50 °C, 30 min	quant.	50	-	-	-	-	50
4	A	4.0	rt, 30 min	80	7	-	26	29	18	13
5	B	0.4	50 °C, 30 min	77	91	-	trace	8	-	-
6 [c]	B	0.4	rt, 30 min	91	91	9	-	-	-	-
7	B	4.0	50 °C, 30 min	63	-	-	38	62	-	-

[a] The ratio was determined by the ^{1}H-NMR analysis. [b] SmI_2 (4 equivalents), prepared from Sm metal and CH_2I_2, was used. [c] HMPA (2 equivalents) was added.

tested: THF was added to a mixture of Sm, I_2 and aziridine substrate followed by addition of DMEA as described in the literature (method A);[18a,b] a mixture of Sm and I_2 in THF was roughly degassed and sonicated. Confirmed the blue color in the reaction mixture, a solution of aziridine and DMEA in THF was added (method B).[18c] At first, the effect of the equivalency of I_2 was examined in method A. When 0.4 equivalent of I_2 was used, the epimerization product (±)-*cis*-**1a** was obtained instead of the desired β-aminoester **17** (run 3). In this case, the ratio of *cis* and *trans* isomers in crude product was *ca.* 1 : 1. Increment of I_2 to 4.0 equivalents lead to the non-selective formation of α-aminoester **18**, dihydrocinnamate **19**, cinnamate **20**,[19] and (±)-*cis*-**1a** (run 4). The indicative blue color of SmI_2 was not observed in each trials in method A. On the other hand, the reaction was retarded in method B with 0.4 equivalent of I_2, even in the presence of HMPA (runs 5, 6). Dihydrocinnamate **19** and α-aminoester **18** were mainly generated with excess amount of I_2 (run 7). In these trials, desired β-aminoester **17** was not obtained as a major product, however, the epimerization of *trans*-aziridine to *cis*-one was observed with 0.4 equivalent of I_2 in method A. To our knowledge, only the epimerization reaction of aziridines in basic,[20] thermal[21,22] and photochemical conditions[22] and that of vinyl aziridines with palladium catalysts[23] were reported.[24] Thus, we explored the epimerization reactions of *trans*-**1a**.[25]

Table 2 Effects of reagents on the epimerization of aziridine (±)-*trans*-**1a**



run	Sm	I_2	DMEA	product ratio [a]			
	(4 eq)	(0.4 eq)	(4.0 eq)	*trans*-**1a**	*cis*-**1a**	*cis*-**21**	**22**
1 [b]	+	+	+	50	50	-	-
2	+	+	-	24 (13)	60 (30)	16 (19)	-
3	-	+	+	45 [c]	54 [c]	-	-
4	-	+	-	40 (24)	40 (32)	-	20 (13) [d]
5	+	-	+	no reaction			

[a] The ratio was determined by the ^{1}H-NMR analysis. The value in parenthesis shows isolated yield after column chromatography (hexane - AcOEt = 20 : 1 to 5 : 1). [b] Run 3 in Table 1. [c] Small amount of unidentified byproducts was contaminated. [d] *Anti* : *syn* = 1.0 : 0.2.

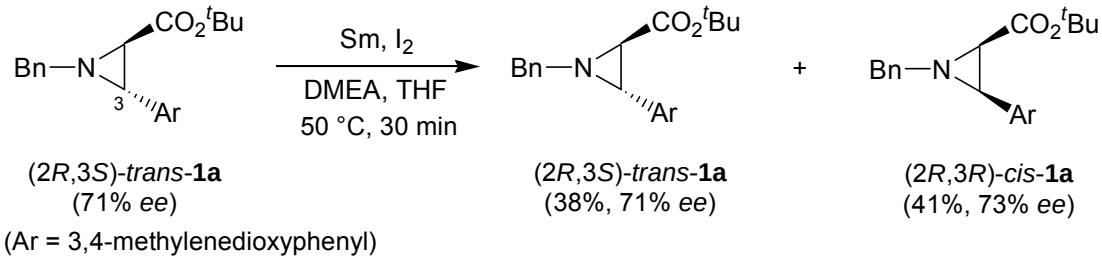
Epimerization reaction of *trans*- to *cis*-aziridinecarboxylates

We next examined the role of reagents in method A (Table 2). Epimerization is predominant in the absence of DMEA, however, amide *cis*-**21** was isolated as a byproduct, which would be derived from (±)-*cis*-**1a** and benzylamine, presumably generated on decomposition of **1a** (run 2). Corresponding *trans*-isomer of **21** was not observed in this experiment. Surprisingly, even in lacking Sm and both of Sm and DMEA, 1 : 1 mixtures of (±)-*cis*- and (±)-*trans*-**1a** were obtained (runs 3, 4). A small amount of unidentified byproducts was contaminated in the former, and ring-opening product **22** was generated as a mixture of diastereoisomers in the latter condition. No reaction was observed in the absence of I_2 (run 5). These results showed that I_2 is crucial for this epimerization.

To identify the epimerized chiral center of *trans*-**1a**, optically active aziridine *trans*-**1a** was subjected to the reaction in method A (Scheme 4). Treatment of (2*R*,3*S*)-*trans*-**1a** (71% *ee*) with Sm/I_2 system afforded a 1 : 1 mixture of *cis*- and *trans*-**1a**. After the separation, absolute configuration of each diastereoisomer was determined as (2*R*,3*S*) for *trans* and (2*R*,3*R*) for *cis* isomer by chiral HPLC analysis,[26] respectively, which shows that the epimerization occurs at benzylic C3 position of *trans*-**1a**.

Next, the effect of the aryl groups at C3 of aziridines was investigated (Table 3). Reactions of *trans*-aziridines with electron-rich aromatics such as 3,4-methylenedioxy- *trans*-**1a** and 3,4-dimethoxyphenyl derivatives *trans*-**1b** gave a 1 : 1 mixture of diastereoisomers (runs 1, 2). Disappointingly, epimerization of 2-indolyl derivative *trans*-**1c** to *cis*-one, a synthon for the aziridinomitosene skeleton, was sluggish (run 3) and phenyl *trans*-**1d** and 4-chlorophenyl derivatives *trans*-**1e** gave no isomerization product (runs 4, 5). These results clearly showed that the electron-donating character of aryl group is important in this epimerization reaction.

Thus, more powerful catalysts were explored with using several Lewis acids (Table 4). Epimerization of (±)-*trans*-**1a** with boron trifluoride etherate ($BF_3{\cdot}OEt_2$) at -60 °C produced a *trans*-major mixture (*cis* : *trans* = *ca.* 1 : 2.3) (run 2). Stronger Lewis acid, such as tin (IV) chloride ($SnCl_4$) was not so effective to give a mixture in the same ratio as the reaction with $BF_3{\cdot}OEt_2$ (run 3). Milder Lewis acid such as zinc iodide (ZnI_2) gave *cis*-major mixture, however, ring opening product **22** was contaminated as a major



(2*R*,3*S*)-*trans*-**1a** (71% *ee*)

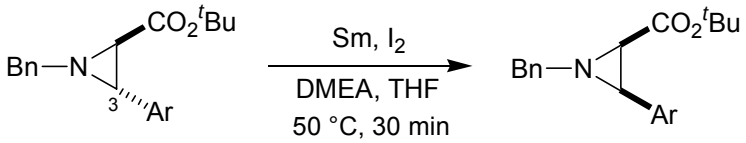
(2*R*,3*S*)-*trans*-**1a** (38%, 71% *ee*)

(2*R*,3*R*)-*cis*-**1a** (41%, 73% *ee*)

(Ar = 3,4-methylenedioxyphenyl)

Scheme 4 Epimerization reaction of optically active aziridine (2*R*,3*S*)-*trans*-**1a** with Sm/I_2 system

Table 3 Effects of aryl group at C3 on the epimerization of aziridine (±)-*trans*-**1**

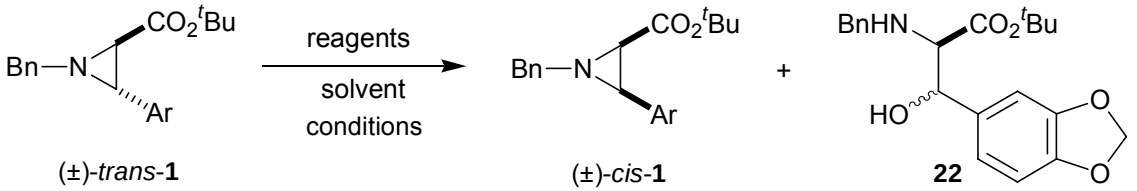


(±)-*trans*-**1** (±)-*cis*-**1**

run	aziridine [a]	product ratio [b] *trans* : *cis*	run	aziridine [a]	product ratio [b] *trans* : *cis*
1 [c]	**1a**	50 : 50	4	**1d**	100 : 0
2	**1b**	52 : 48	5	**1e**	100 : 0
3	**1c**	83 : 17			

[a] Ar in aziridines **1** correspond to those in Scheme 1. [b] The ratio was determined by the ^{1}H-NMR analysis. [c] Run 3 in Table 1.

Table 4 Effects of reagents on the epimerization of aziridine *trans*-**1**



(±)-*trans*-**1** (±)-*cis*-**1**

run	aziridine [a]	reagents (eq)	solvent	condition	crude yield (%)	product ratio [b] *trans*-**1**	*cis*-**1**	**22**
1 [c]	**1a**	Sm (4), I_2 (0.4), DMEA (4)	THF	50 °C, 30 min	quant.	50	50	-
2	**1a**	BF_3·OEt_2 (1.0)	CH_2Cl_2	-60 °C, 3.5 h	quant.	70 (60)	30 (25)	-
3	**1a**	$SnCl_4$ (1.0)	CH_2Cl_2	-60 °C, 1 h	95	70	30	-
4	**1a**	ZnI_2 (0.8)	CH_2Cl_2	0 °C, 2 h	97	29	14	57 [d]
5	**1a**	$InCl_3$ (0.7)	CH_2Cl_2	rt, 30 min	98	36	64	-
6	**1a**	$InCl_3$ (0.2)	CH_2Cl_2	rt, 30 min	quant.	30	70	-
7	**1a**	$InCl_3$ (0.2)	CH_2Cl_2	rt, 1 d	quant.	30	70	-
8	**1a** [e]	$InCl_3$ (0.3)	CH_2Cl_2	rt, 20 min	quant.	30 [e]	70 [f]	
9	**1c**	$InCl_3$ (0.2)	CH_2Cl_2	rt, 1 h	quant.	48 (44)	52 (43)	-

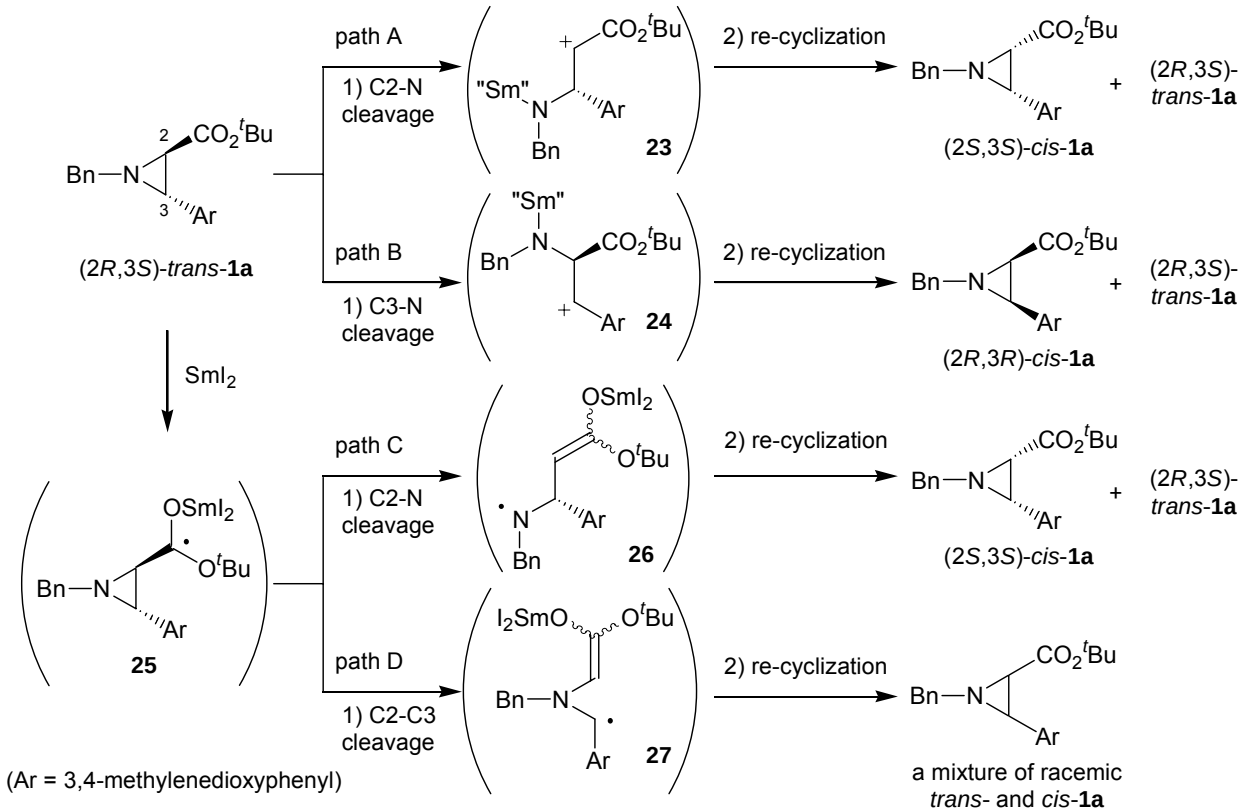
[a] Ar in aziridines **1** correspond to those in Scheme 1. [b] The ratio was determined by the ^{1}H-NMR analysis. The value in parenthesis shows isolated yields after column chromatography. [c] Run 3 in Table 1. [d] *Anti* : *syn* = 1.0 : 0.1. [e] (2*R*,3*S*)-isomer (76% ee). [f] (2*R*,3*R*)-isomer (76% ee).

product (*cis*-**1a** : *trans*-**1a** : **22** = *ca.* 2 : 1 : 4) (run 4). Next, indium chloride ($InCl_3$), effective catalyst for the ring opening of "activated"[27] and "unactivated"[6] aziridines, was applied. As a result, *cis*-major mixture (*cis* : *trans* = *ca.* 1.8 : 1) of **1a** was obtained without any formation of byproduct (run 5). The ratio of the epimeric products was not affected by the decrease of the reagent from 0.7 to 0.2 equivalent (run 6) or longer reaction period to 1 day (run 7). Epimerization at C-3 position of **1a** was confirmed by conversion of (2*R*,3*S*)-*trans* to (2*R*,3*R*)-*cis* isomer (run 8). The epimerization of *trans*-indolylaziridine **1c** with $InCl_3$ gave a *ca.* 1 : 1 mixture of *cis*- and *trans*-**1c** (run 9).

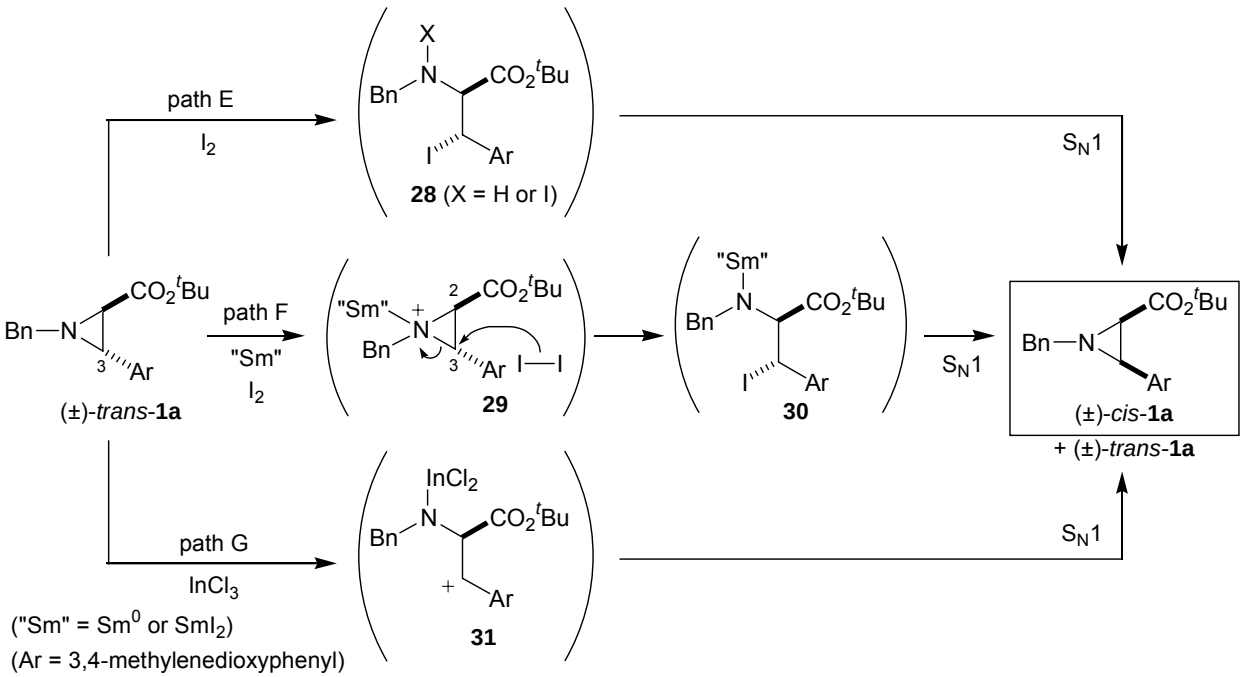
DISCUSSION

The epimerization of *trans*-**1a** with Sm/I_2 system could be proceeded in mainly two steps: 1) ring opening, 2) re-cyclization, and via four pathways (Scheme 5): cationic cleavage of aziridine *trans*-**1a** at C2-N (to **23**, path A) and C3-N bonds (to **24**, path B), and single-electron reduction on the carbonyl group to ketyl radical **27** and cleavage at C2-N (to **25**, path C) and C2-C3 bonds (to **26**, path D). The result with optically active *trans*-aziridine (2*R*,3*S*)-*trans*-**1a** to *cis*-one (2*R*,3*R*)-**1a** (Scheme 4) supports path B.

The results of runs 2-4 in Table 2 showed the important role of I_2. Furthermore, the epimerization was not observed when I_2 was completely consumed for the preparation of SmI_2 in method B (run 5 in Table

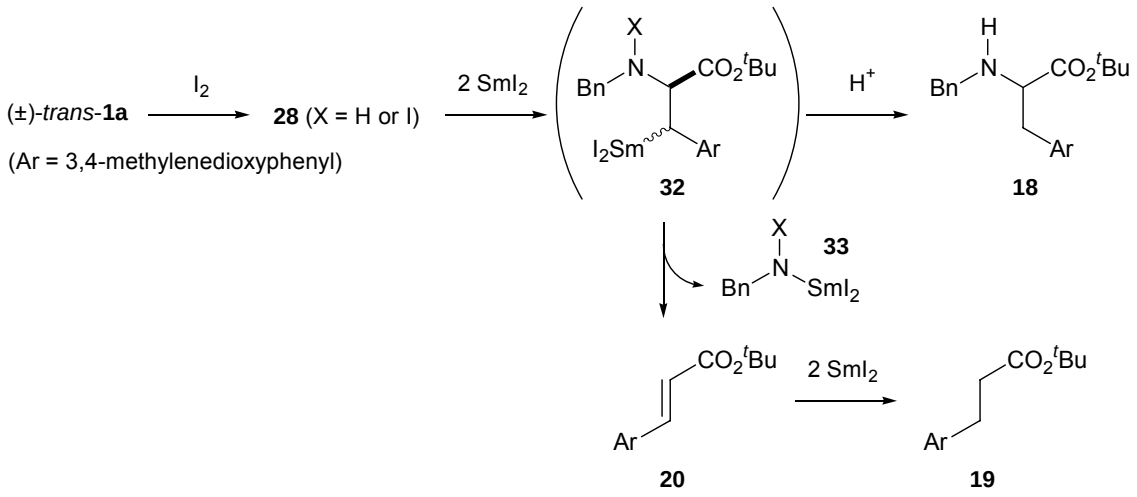


Scheme 5 Possible pathways of the epimerization of *trans*- to *cis*-aziridine **1a**



Scheme 6 Proposed mechanisms of epimerization of *trans*-**1a** via C3-N bond cleavage

1). From these results, the selective cleavage of benzylic C3-N bond mediated by I_2 (path E in Scheme 6) to iodide **28** and S_N1-type re-cyclization were proposed as a reaction mechanism. Sm species could act as Lewis acid towards **1a** to promote the ring-opening step via aziridinium **29** to iodide **30** (path F). Reaction with other Lewis acids such as $InCl_3$ is considered to proceed through C3-N bond cleavage of *trans*-**1a** to cationic intermediate **31** followed by re-cyclization (path G). For the moment, the reason why $InCl_3$ gave the best result is not clear.



Scheme 7 Proposed mechanism for the generation of hydrogenated products **18** and **19**

On the other hand, the main products of the reaction with excess mount of I_2 are hydrogenated products such as **18** and **19** (runs 4 and 7 in Table 1). Selective C3-N bond cleavage of aziridine *trans*-**1a** with I_2 and reduction of corresponding iodide **28** with SmI_2 would furnish organosamarium species **32**, which would be protonated to α-aminoester **18**. Elimination of samarium amide **33** from **32** to cinnamate **20** followed by reduction with SmI_2 would give dihydrocinnamate **19** (Scheme 7).

CONCLUSION

In conclusion, we found the epimerization conditions of *trans* to *cis* isomer of 3-arylaziridine-2-carboxylates. In the preliminary trials, a combination of Sm, I_2, and DMEA was found to be effective, in which I_2 is crucial in this epimerization. The reaction with optically active aziridine suggested the epimerization at benzylic C3 position. $InCl_3$ was found to be the most effective Lewis acid for the epimerization of aziridines with electron-rich aromatics as well as indolyl group.[28] Application of this system to the synthesis of *cis*-aziridine-containing natural products such as mitomycins is under investigation.

EXPERIMENTAL

General: All melting points were measured on Yanagimoto MPSI melting point apparatus and are uncorrected. IR spectra were recorded in neat or with Attenuated Total Reflectance (ATR) system on a JASCO FT / IR-300E spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-GSX-400α, JNM-ECP-400, JNM-GSX-500α, JNM-ECP-600 unless otherwise stated. MS spectra were measured on JEOL JNM MS-GCMATE for EIMS, and JEOL JMS-HX110 or JEOL JMS-AX505 for FABMS. Ultrasonic stirrer, a Nihonseiki Youkai-kun, USS-1, was used for sonication. For column chromatography was used Kanto Chemical silica gel 60 spherical. For TLC were used Merck Art 5715 DC-Fertigplatten Kieselgel 60 F_{254}. Anhydrous CH_2Cl_2 and THF were purchased from Kanto Chemical and Wako Chemical, respectively. Samarium metal (Sm) was purchased from Nippon Yttrium Co. Ltd. as ingot and was used after grind and washing with hexane and methanol, successively, and dried.

1*H*-Indole-2-carboxyaldehyde (10)

A solution of ethyl indole-2-carboxylate (3.00 g, 15.9 mmol) in THF (18 mL) was added to a suspension of $LiAlH_4$ (3.03 g, 79.8 mmol) in THF (18 mL) at 0 °C and the whole was stirred at 0 °C for 30 min. H_2O (5 mL), 20% NaOH (5 mL), and H_2O (20 mL) was added successively at 0 °C. The whole was diluted with CH_2Cl_2-CH_3OH (8 : 1, 50 mL) and was stirred at rt for 1 h. The mixture was filtered off through a pad of Celite pad and the filtrate was washed with brine (3 x 40 mL) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to leave alcohol **9** as pale yellow solids (2.32 g, 99%). The crude **9**

was dissolved in CH_2Cl_2 (75 mL) and MnO_2 (13.2 g, 152 mmol) was added. After stirring at rt for 14 h, the whole was filtered off through a pad of Celite® and the precipitate was washed with CH_2Cl_2. The filtrate and the washing was combined and evaporated *in vacuo* to give aldehyde **10** as brown solid (1.77 g, 79%), which was used for next step without further purification.

1-(*p*-Toluenesulfonyl)-1*H*-indole-2-carboxyaldehyde

A solution of aldehyde **10** (2.35 g, 16.2 mmol) in DMF (9 mL) was added to a suspension of NaH (60%, 976 mg, 24.4 mmol) in DMF (15 mL) at 0 °C and the whole was stirred at rt for 30 min. A solution of *p*-toluenesulfonyl chloride (4.32 g, 22.7 mmol) in DMF (7 mL) was added at 0 °C and the whole was stirred at 0 °C for 2 h. H_2O (25 mL) was added at 0 °C and the whole was extracted with AcOEt (5 x 40 mL). The combined organic layer was washed with H_2O (10 x 1.5 mL) and brine (5 x 1.5 mL) and was dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by silica gel (SiO_2) column chromatography (CC) (hexane : benzene = 1 : 2) to give pale yellow solids (2.95 g, 61%). mp 136.5 - 137.5 °C. IR (ATR, cm^{-1}) 1674 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 2.33 (3H, s, CH_3), 7.20 (2H, d, *J* = 8.3 Hz, Ts-meta-H_2), 7.32 (1H, t, *J* = 7.6 Hz, H-6), 7.47 (1H, s, H-3), 7.53 (1H, t, *J* = 7.3 Hz, H-5), 7.63 (1H, d, *J* = 8.1 Hz, H-7), 7.66 (2H, d, *J* = 8.3 Hz, Ts-ortho-H_2), 8.24 (1H, d, *J* = 8.6 Hz, H-4), 10.54 (1H, s, CHO). ^{13}C-NMR (100 MHz) δ (ppm): 21.5, 115.3, 118.8, 123.6, 124.8, 126.6, 128.1, 128.89, 129.9, 134.6, 137.7, 138.4, 145.6, 183.3. HREIMS *m/z* 299.0641 (Calcd for $C_{16}H_{13}NO_3S$: 299.0616).

Synthesis of indolylaziridinecarboxylates 1c

A mixture of aldehyde **6c** (150 mg, 0.50 mmol) and guanidinium salt **4** (240 mg. 0.60 mmol) in THF (0.5 mL) was sonicated until complete dissolution of **6a** and **4**. Freshly distilled TMG (0.08 mL, 0.64 mmol) was added at rt and the whole was stirred at rt for 23 h. The whole was dissolved in MeCN (10 mL) and SiO_2 (Fuji silicia, FL100D, 3.0 g) was added. The mixture was stirred at rt for 1 day. After the suction filtration of the SiO_2, the residue was washed with $CHCl_3$. The filtrate and the washings were combined and the whole was evaporated *in vacuo*. The residue was purified br CC (hexane - AcOEt = 15 : 1) to give *trans*-**1c** as a yellow oil (169 mg, 67%) and *cis*-**1c** as a yellow oil (13 mg, 5%)

(2*RS*,3*RS*)-*tert*-Butyl [1-benzyl-3-(1-*p*-toluenesulfonyl-1*H*-indol-2-yl)aziridine-2-carboxylate (*trans*-1c)

IR (ATR, cm^{-1}) 1722 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 1.46 [9H, s, $C(CH_3)_3$], 2.32 (3H, s, CH_3), 2.76 (1H, br s, C2H), 3.83 (1H, br s, C3H), 4.16, 4.40 (each 1H, d, *J* = 13.9 Hz, PhC$\underline{H_2}$), 6.54 (1H, s, indole C3H), 7.14-7.44 (total 10H, m, Ar), 7.76 (2H, d, *J* = 8.1 Hz, Ts-ortho-H_2), 8.11 (1H, d, *J* = 8.2 Hz, indole C4H). ^{13}C-NMR (100 MHz) δ (ppm): 21.5, 28.0, 42.9, 44.1, 54.6, 82.0, 109.5, 114.3, 120.9,

123.6, 124.5, 126.6, 126.9, 128.21, 128.25, 129.1, 129.8, 135.8, 136.9, 138.6, 139.2, 144.8, 167.4. HREIMS *m/z* 502.1923 (Calcd for $C_{29}H_{30}N_2O_4S$: 502.1926).

(2*RS*,3*SR*)-*tert*-Butyl [1-benzyl-3-(1-*p*-toluenesulfonyl-1*H*-indol-2-yl)aziridine-2-carboxylate (*cis*-1c)

IR (ATR, cm^{-1}) 1738 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 1.19 [9H, s, $C(CH_3)_3$], 2.31 (3H, s, CH_3), 2.69 (1H, d, *J* = 6.4 Hz, C2H), 3.58 (1H, d, *J* = 6.4 Hz, C3H), 3.82, 3.90 (each 1H, d, *J* = 13.9 Hz, PhC$\underline{H}_2$), 6.74 (1H, s, indole C3H), 7.14-7.36 (total 7H, m, Ar), 7.42 (2H, diffused t, *J* = 7.6 Hz, Ar), *7*.74 (2H, d, *J* = 8.4 Hz, Ts-ortho-H_2), 8.00 (1H, d, *J* = 8.2 Hz, indole C4H). ^{13}C-NMR (100 MHz) δ (ppm): 21.5, 27.7, 42.1, 47.2, 63.3, 81.3, 111.7, 114.1, 120.9, 123.4, 12435, 126.7, 127.2, 127.9, 128.4, 129.1, 129.8, 135.5, 135.8, 136.7, 137.9, 144.7, 167.2. HREIMS *m/z* 502.1934 (Calcd for $C_{29}H_{30}N_2O_4S$: 502.1926).

General procedure for the trials towards reductive ring opening of *trans*-1a with Sm/I_2 system (method A, run 3 in Table 1)

To a mixture of Sm (92 mg, 0.61 mmol), I_2 (16 mg, 0.06 mmol) and *trans*-**1a** (53 mg, 0.15 mmol) under Ar atmosphere, THF (1 mL) and DMEA (0.06 mL, 0.60 mmol) were added at rt and the whole was stirred vigorously at 50 °C for 30 min. After cooling, 10% aq. $Na_2S_2O_3$ (5 mL) was added and the whole was filtered through a pad of Celite. The filtrate was extracted with AcOEt (2 x 20 mL). The combined organic layers were combined and was washed with saturated aq. $NaHCO_3$ (2 x 5 mL), H_2O (2 x 5 mL), and brine (2 x 5 mL), successively, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was analyzed by ^{1}H-NMR to be a 1 : 1 mixture of *trans*- and *cis*-**1a**.

General procedure for the trials towards reductive ring opening of *trans*-1a with Sm/I_2 system (method B, run 6 in Table 1)

To a mixture of Sm (92 mg, 0.61 mmol), I_2 (16 mg, 0.06 mmol), THF (1.0 mL) was added and the whole was roughly vacuumed with stirring and sonication at rt. After 20 min, color of the mixture changed to dark blue. HMPA (0.05 mL, 0.29 mmol) was added and the color of the mixture changed to purple. After stirring for 15 min, a solution of *trans*-**1a** (50 mg, 0.14 mmol) and DMEA (0.06 mL, 0.60 mmol) in THF (1.0 mL) was added at rt and the whole was stirred at rt for 30 min. 10% aq. $Na_2S_2O_3$ (5 mL) was added and the whole was filtered through a pad of Celite. The filtrate was extracted with AcOEt (2 x 20 mL). The combined organic layers were combined and was washed with saturated aq. $NaHCO_3$ (2 x 5 mL), H_2O (2 x 5 mL), and brine (2 x 5 mL), successively, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was analyzed by ^{1}H-NMR to be a mixture of *trans*-**1a** and **17** (91 : 9).

(±)-*tert*-Butyl 3-benzylamino-3-(3,4-methylenedioxyphenyl)propionate (17)

A colorless oil. IR (neat, cm^{-1}) 3332 (N-H), 1719 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 1.38 [9H, s, $C(CH_3)_3$], 2.48 (1H, dd, *J* = 15.3, 5.2 Hz, one of $C\underline{H}_2CO$), 2.58 (1H, dd, *J* = 15.3, 8.7 Hz, one of $C\underline{H}_2CO$), 3.53, 3.64 (each 1H, d, *J* = 13.2 Hz, $PhC\underline{H}_2$), 4.00 (1H, dd, *J* = 8.7, 5.2 Hz, CH), 5.95 (2H, s, OCH_2O), 6.75-6.81 (2H, m, Ar), 6.91 [1H, d, *J* = 1.5 Hz, Ar(2)-H], 7.21-7.32 (5H, m, Ar). ^{13}C-NMR (100 MHz) δ (ppm): 28.0, 44.4, 51.3, 58.9, 80.7, 100.9, 107.2, 108.0, 120.6, 126.8, 128.1, 128.3, 136.8, 140.3, 146.7, 147.8, 171.0. HRFABMS *m/z* 356.1829 (Calcd for $C_{21}H_{26}NO_4$: 356.1862).

(±)-*tert*-Butyl 2-benzylamino-3-(3,4-methylenedioxyphenyl)propionate (18)

A colorless oil. IR (neat, cm^{-1}) 3334 (N-H), 1722 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 1.40 [9H, s, $C(CH_3)_3$], 2.82 (1H, dd, *J* = 13.7, 7.1 Hz, one of $C\underline{H}_2Ar$), 2.86 (1H, dd, *J* = 13.7, 6.6 Hz, one of $C\underline{H}_2Ar$), 3.35 (1H, dd, *J* = 7.1, 6.6 Hz, CH), 3.64, 3.81 (each 1H, d, *J* = 12.9 Hz, $PhC\underline{H}_2$), 5.92 (2H, s, OCH_2O), 6.64 [1H, dd, *J* = 7.8, 1.7 Hz, Ar(6)-H], 6.70 [1H, d, *J* = 1.7 Hz, Ar(2)-H], 6.71 [1H, d, *J* = 7.8 Hz, Ar(6)-H], 7.21-7.32 (5H, m, Ar). ^{13}C-NMR (100 MHz) δ (ppm): 28.1, 39.5, 52.0, 62.7, 81.2, 100.8, 108.0, 109.8, 122.4, 127.0, 128.2, 128.4, 131.3, 146.2, 147.4, 173.9. HRFABMS *m/z* 356.1886 (Calcd for $C_{21}H_{26}NO_4$: 356.1862).

***tert*-Butyl 3-(3,4-methylenedioxyphenyl)propionate (19)**

A colorless oil. IR (neat, cm^{-1}) 1724 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 1.43 [9H, s, $C(CH_3)_3$], 2.49 (2H, t, *J* = 8.0 Hz, $C\underline{H}_2CO$), 2.82 (2H, t, *J* = 8.0 Hz, $C\underline{H}_2Ar$), 5.92 (2H, s, OCH_2O), 6.65 [1H, dd, *J* = 8.0, 2.0 Hz, Ar(6)-H], 6.69 [1H, d, *J* = 2.0 Hz, Ar(2)-H], 6.72 [1H, d, *J* = 8.0 Hz, Ar(5)-H]. ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 28.2, 30.9, 37.4, 80.4, 100.8, 108.1, 108.8, 121.1, 134.6, 145.8, 147.6, 172.2. HREIMS *m/z* 250.1199 (Calcd for $C_{14}H_{18}O_4$: 250.1205).

(*E*)-*tert*-Butyl 3-(3,4-methylenedioxyphenyl)acrylate (20)

Colorless needles. mp 79-81 °C (lit.,[19] 79-80 °C). IR (neat, cm^{-1}) 1739 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 1.53 [9H, s, $C(CH_3)_3$], 6.00 (2H, d like, *J* = ,1.1 Hz, OCH_2O), 6.19 (1H, d, *J* = 15.9 Hz, C2-H), 6.80 [1H, d, *J* = 8.1 Hz, Ar(5)-H], 6.67 [1H, diffused dd, *J* = 8.1, 1.5 Hz, Ar(6)-H], 6.99 [1H, diffused d, *J* = 1.5 Hz, Ar(2)-H], 7.49 (1H, d, *J* = 15.9 Hz, C3-H).

(2*RS*,3*RS*)-*N*,*N*'-Dibenzyl-3-(3,4-methylenedioxyphenyl)aziridine-2-caroboxamide (*cis*-21)

A yellow oil. IR (ATR, cm^{-1}) 3376 (N-H), 1664 (C=O). ^{1}H-NMR (400 MHz) δ (ppm): 2.26 (1H, d, *J* = 7.0 Hz, C2H), 3.11 (1H, d, *J* = 7.0 Hz, C3H), 3.61, 3.81 (each 1H, d, *J* = 13.0 Hz, $PhC\underline{H}_2$), 4.00 (1H, dd, *J* = 15.0, 7.3 Hz, one of $PhC\underline{H}_2$), 4.38 (1H, dd, *J* = 15.0, 4.9 Hz, one of $PhC\underline{H}_2$), 5.90, 5.91 (each 1H, d, *J*

= 1.5 Hz, one of OCH_2O), 6.53 (1H, brt, *J* = 5.8 Hz, NH), 6.64 [1H, d, *J* = 8.1 Hz, Ar(5)-H], 6.69 [1H, d, *J* = 1.5 Hz, Ar(2)-H], 6.72-6.74 (3H, m, Ar), 7.15-7.18 (3H, m, Ar), 7.31-7.36 (5H, m, Ar). ^{13}C-NMR (100 MHz) δ (ppm): 42.6, 46.6, 47.5, 63.3, 101.0, 108.2, 108.3, 121.1, 127.0, 127.2, 127.7, 128.3, 128.4, 128.7, 128.9, 137.7, 137.8, 147.0, 147.5, 167.6. HRFABMS *m/z* 387.1729 (Calcd for $C_{24}H_{23}N_2O_3$: 387.1709).

General procedure for the isomerization of aziridine *trans*-1a with $InCl_3$ (run 7 in Table 4)

To a mixture of *trans*-**1a** (41 mg, 0.12 mmol) and $InCl_3$ (6 mg, 0.027 mmol), CH_2Cl_2 (1.5 mL) was added and the whole was stirred at rt for 25 min. Sat. aq. $NaHCO_3$ (5 mL) was added and the whole was extracted with CH_2Cl_2 (4 x 6 mL). The organic layers were combined and the whole was washed with H_2O (2 x 6 mL) and brine (2 x 6 mL), successively, and dried over K_2CO_3. The solvent was evaporated *in vacuo* and the residue was analyzed by ^{1}H-NMR to be a mixture of *trans*- and *cis*-**1a** (30 : 70).

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