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β-Amino Esters from the Reductive Ring Opening of Aziridine-2-carboxylates

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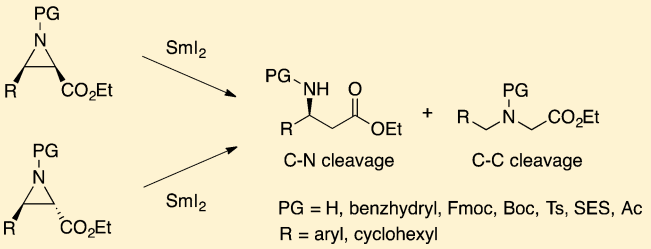
Supporting Information

ABSTRACT: A general study is undertaken to examine the scope of the reductive ring opening of aziridine-2-carboxylates with samarium diiodide. The competition between C−C and C−N bond cleavage is examined as a function of the nature of the N-substituent of the aziridine, the nature of the substituent in the 3-position of the aziridine, and whether the substituent in the 3-position is in a cis or trans relationship with the carboxylate in the 2-position. The desired C−N bond cleavage leads to β-amino esters that are the predominant products for most aziridines with an N-activating group. However, C−C cleavage products are observed with an aryl group in the 3-position; this can be particularly pronounced with *cis*-aziridines where a nearly equal mixture of the two is observed. Exclusive formation of the C−N cleavage product is observed for all aziridines with the strongly N-activating *p*-toluene sulfonate group. Similarly high selectivity is observed for the 2-trimethylsilylethyl sulfonate group (SES), which is easier to remove. The utility of these methods is illustrated in the synthesis of protected forms of (*R*)-β^3-DOPA and L-DOPA from the same aziridine, the former by SmI_2-mediated reductive opening at C-2 and the latter by palladium-mediated reductive opening at C-3.

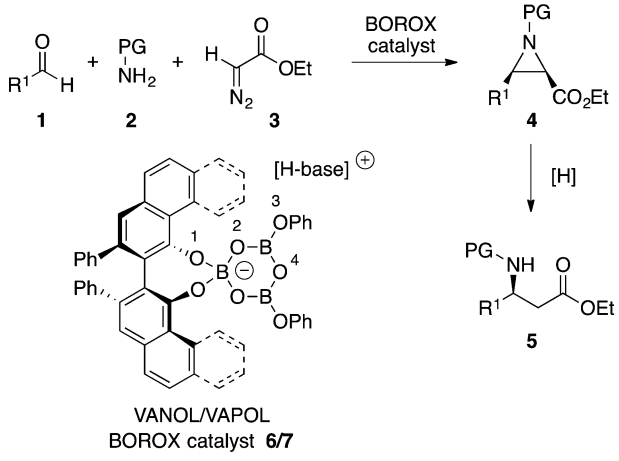


1. INTRODUCTION

The synthesis of β-amino acids has been a subject of great interest and importance for quite some time[1] but especially because it was discovered[2] that β-peptides derived from β-amino acids have many of the properties of α-peptides but are much more proteolytically stable. There has been a decided uptick in the efforts to develop catalytic asymmetric methods for the synthesis of β-amino acids in the past decade.[3] Our interest in this area follows from our experiences in the development of the catalytic asymmetric synthesis of aziridines.[4] We have found that aziridines can be prepared with a high degree of enantio- and diastereoselection by a three-component coupling of an aldehyde, an amine, and ethyl diazoacetate under the aegis of a BOROX catalyst (Scheme 1).[5,6] High yields of aziridine-2-carboxylates can be realized starting with aryl, alkyl, or alkynyl aldehydes with a typical selectivity for the cis isomer of ≥50:1.[7] The enantioselection can depend on the nature of the amine substitutent[7d] or on the nature of the ligand; with the right combination, a minimum of 96% ee can be obtained with aryl, alkynyl, and first, second, and third degree aliphatic aldehydes.[7,8] The diastereoselection for the aziridine can be switched to trans with the use of a diazoacetamide.[9] The purpose of the present work is to explore the reductive opening of *cis*-aziridine-2-carboxylates, with the goal of directing opening at the C-2 position to provide for an efficient and highly stereoselective catalytic asymmetric route to β-amino esters.

A number of methods are known for the reductive opening of aziridine-2-carboxylates to give β-amino esters.[10,11] The nature of the reducing agent can be quite critical when it comes to aziridines with an aryl group in the 3-position. As illustrated in Scheme 2, such aziridines are prone to reductive opening, resulting in α-amino esters by hydrogenolysis or Lewis or Brønsted acid-mediated reduction.[10,12] However, this proclivity for reduction can be reversed by using electron-transfer reduction methods; because the electron preferentially adds to the carbonyl function, it directs ring opening to the 2-position, resulting in β-amino esters. This has been reported with samarium diiodide[13] and magnesium metal.[14] Interestingly, the use of manganese(0) to reduce 3-arylaziridine-2-carboxamides

Scheme 1



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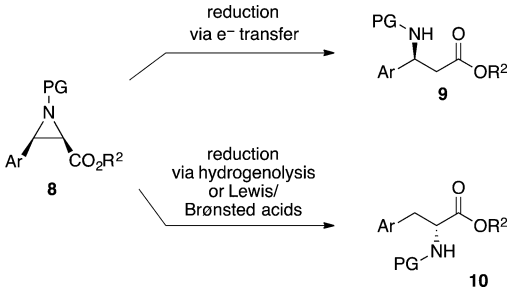
Scheme 2



occurs with opening at the 3-position to give α-amino amides,[15] whereas the same substrates are reduced to β-amino amides by samarium diiodide.[13b] In a non-electron-transfer process, tributyltin hydride is known to open aziridinyl ketones to give β-amino ketones in a radical process.[16] In a distinct and mechanistically different reaction, the addition of silyl anions to 2-aziridinyl ketones leads to β-amino ketones via an addition, Brook rearrangement, and anionic induced-ring opening.[17]

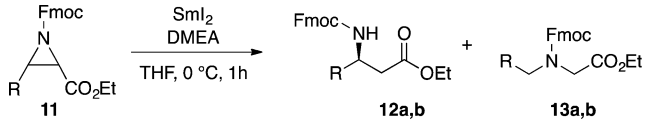
2. RESULTS AND DISCUSSION

Whereas 3-arylaziridine-2-carboxylates can be reductively opened to β-amino esters with either samarium diiodide or magnesium(0), all examples in the literature are with trans isomers of the aziridine.[13,14] Because the BOROX catalyst produces very high selectivities for *cis*-aziridines, it became imperative to determine if the same regioselectivities observed in the reductive opening of *trans*-aziridines would translate to *cis*-aziridines. We also began our studies with Fmoc aziridines because this would be the most desirable N-substituent for the purposes of solid-state synthesis of β-peptides. Fmoc aziridine *cis*-**11a** has a phenyl group in the 3-position *cis* to the ethyl carboxylate, and its reductive ring opening was examined with both magnesium in methanol and samarium diiodide in the presence of *N*,*N*-dimethylethanol amine (DMEA). The purpose of DMEA is to sequester the samarium(III) that formed and prevent it from opening the aziridine as a Lewis acid giving α-amino ester product **14a**.[13a,b] The reduction with magnesium did not occur under the reported conditions (−23 °C, Fmoc aziridines were not included in the literature study),[14] and high conversion was realized only after prolonged heating at 55 °C. However, no α-cleavage product **12a**, β-cleavage product **14a**, or C−C cleavage product **13a** was observed in the crude reaction mixture. The products that were formed were not separated and identified. The same result was obtained with two different batches of commercial magnesium powder. The reduction of *cis*-**11a** with samarium diiodide was performed under the reported conditions[13a,b] indicated in Scheme 3, and the result was that both α-cleavage product **12a** and C−C cleavage product **13a** were formed in substantial amounts.

The reductive ring opening of *cis*-**11a** could be brought to completion with 4 equiv of SmI_2 and 8 equiv of DMEA in THF in 1 h at 0 °C (Table 1, entry 1). This reaction resulted in the isolation of α-cleavage product **12a** in 45% yield and C−C cleavage product **13a** in 46% yield.[18] Upon examining the reductive ring opening of the corresponding *trans*-aziridine *trans*-**11a** under the optimized conditions, it became clear that the product distribution greatly depends on the stereochemistry of the aziridine. The *cis*-aziridine **11a** gives a 1:1 mixture of **12** and **13**, whereas the *trans*-aziridine **11a** gives a 16.7:1 mixture of **12** and **13** (Table 1, entries 1 and 3, respectively). This was not the case with aziridines bearing an alkyl group in the 3-position. Both the cis and trans isomers of 3-cyclohexyl aziridine **11b** gave exclusive opening at the α-position and a highly selective formation of β-amino ester **12b** (Table 1, entries 2 and 4, respectively).

In the search for a more general reductive ring-opening method for converting aziridines to β-amino esters, a number of different N-protecting groups were examined. The results of this analysis are presented in Table 2. As a carbamate, it was not

Table 1. Reductive Opening of *cis*- and *trans*-Fmoc Aziridines[a]



entry	aziridine	R	**12**/**13**[b]	% yield **12**	% yield **13**[d]
1[e]	*cis*-**11a**	phenyl	1:1	45	46[c]
2[e]	*cis*-**11b**	cyclohexyl	>99:1	89	<1
3[f]	*trans*-**11a**	phenyl	16.7:1	82[d]	5
4[g]	*trans*-**11b**	cyclohexyl	>99:1	73[d]	<1

[a]Unless otherwise specified, all reactions were run with 0.2 mmol of aziridine in THF (0.07 M) with 4 equiv of SmI_2 and 8 equiv of DMEA at 0 °C for 1 h and went to completion. [b]Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c]Isolated yield after silica-gel chromatography. [d]Yield from the ^{1}H NMR spectrum of the crude reaction mixture with an internal standard. [e]Data previously reported in ref 18. [f]Reaction with 5.5 equiv of SmI_2 and 11 equiv of DMEA. [g]Reaction with 6 equiv of SmI_2 and 12 equiv of DMEA.

Scheme 3

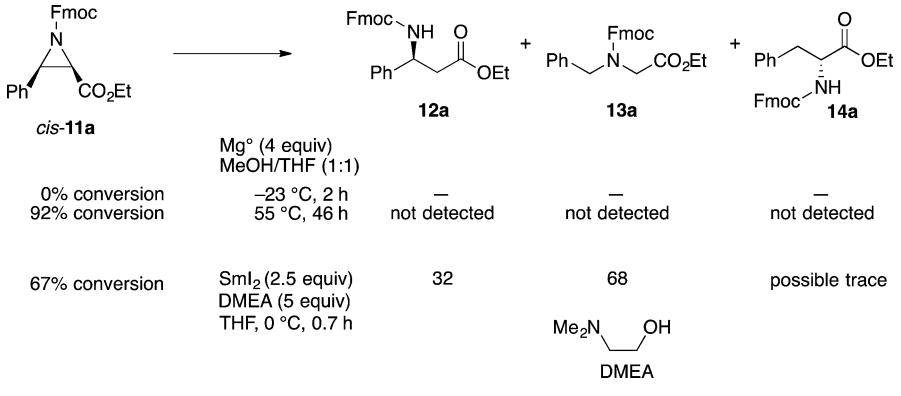


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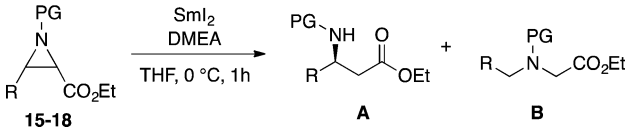
Table 2. Reductive Opening of *cis*- and *trans*-*N*-Activated Aziridines[a]



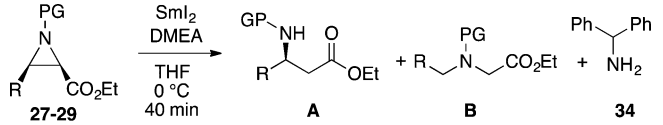
entry	PG	aziridine	R	A/B[b]	% yield A[c]	% yield B[c]
1	Boc	*cis*-**15a**	phenyl	1.4:1	55 (**19a**)	32 (**23a**)
2	Boc	*cis*-**15b**	cyclohexyl	>99:1	84 (**19b**)	(**23b**)
3	Boc	*trans*-**15a**	phenyl	6.7:1	85 (**19a**)	10 (**23a**)
4	Boc	*trans*-**15b**	cyclohexyl	>99:1	84 (**19b**)[d]	(**23b**)
5	Ts	*cis*-**16a**	phenyl	>99:1	93 (**20a**)[e]	(**24a**)
6	Ts	*cis*-**16b**	cyclohexyl	>99:1	97 (**20b**)[f]	(**24b**)
7	Ts	*trans*-**16a**	phenyl	>99:1	88 (**20a**)	(**24a**)
8	Ts	*trans*-**16b**	cyclohexyl	>99:1	95 (**20b**)	(**24b**)
9	SES	*cis*-**17a**	phenyl	23:1	84 (**21a**)[g]	4 (**25a**)
10	Ac	*cis*-**17b**	phenyl	>99:1	52 (**21b**)[h]	(**25b**)

[a]Unless otherwise specified, all reactions were run with 0.2 mmol of aziridine in THF (0.07 M) with 6 equiv of SmI_2 and 12 equiv of DMEA at 0 °C for 1 h and were allowed to go to completion. [b]Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c]Isolated yield after silica-gel chromatography. [d]Yield from the ^{1}H NMR spectrum of the crude reaction mixture with an internal standard. [e]Data taken from ref 18. [f]Reaction with 5 equiv of SmI_2 and 10 equiv of DMEA. [g]A small amount (~6%) of SES-protected benzylamine was also observed. [h]Reaction with 4 equiv of SmI_2 and 8 equiv of DMEA. The ring-opening product from N−C3 cleavage to give an α-amino ester was obtained in 13% isolated yield.

surprising to find that the profile for the SmI_2-mediated reductive ring opening of the Boc-protected aziridines closely matched that for the Fmoc aziridines, with just slightly lower selectivities. The ring opening of phenyl-substituted *cis*-aziridine was not selective (1.4:1, Table 2, entry 1). Phenyl-substituted *trans*-aziridine **15a** was more selective at 6.7:1 (entry 3)[13e], and both isomers of cyclohexyl-substituted aziridine **15b** were highly selective (Table 2, entries 2 and 4). Clearly, the most felicitous N-protecting group, with regard to the selectivity of reductive ring opening by samarium diiodide, is the tosyl group. The profile observed is flat, with >99:1 selectivity for the β-amino ester; *cis*- and *trans*-aziridines and phenyl- and cyclohexyl-substituted aziridines were all in very high yields (Table 2, entries 5−8). The SES (trimethylsilyl ethyl sulfonyl) group[19] is an attractive activating group for an amino function because it is easier to remove than tosyl and has excellent selectivity for the β-amino ester **21a**, as seen with *cis*-aziridine **17a** (23:1, Table 2, entry 9). The slightly lower selectivity of the SES group, as compared to that of the tosyl group (Table 2, entries 5 and 9, respectively), could be expected for an alkyl sulfonate compared to an aryl sulfonate (vide infra). It was also found that the N-acetyl group is capable of delivering high selectivity for β-amino ester **22a** over the C−C cleavage product in the ring opening of *cis*-phenyl aziridine *cis*-**18a**. However, the isolated yield of β-amino ester **22a** was only moderate; the reaction occurs with the formation of 13% of the α-amino ester corresponding to **14** in Scheme 3 (Table 2, entry 10). The latter may result from initial electron transfer to the amide carbonyl followed by the ring opening to a benzyl radical (or anion, vide infra).

Because this is the class of aziridines that the BOROX catalysts are most efficient at producing, the reductive ring opening of unactivated aziridines by samarium diiodide would be a very useful reaction (Scheme 1). Kumamoto and coworkers examined the samarium diiodide-mediated ring opening of *trans*-aziridine-2-carboxylates with an aryl group in the 3-position and a benzyl group on the aziridine nitrogen and found that β-amino esters could be obtained only in very low yields.[13d] The corresponding *cis*-aziridines were not investigated. The present work finds that if samarium diiodide is generated from samarium metal and iodine instead of methylene iodide, it results in the isomerization of *trans*-aziridine to a mixture of *cis*- and *trans*-aziridines. There are no other examples of the reductive ring opening of aziridines bearing an alkyl group on the nitrogen with samarium diiodide in which the aziridines have a carbonyl group in the 2-position and either an aryl or alkyl substituent in the 3-position. On the basis of this, we decided to probe the first examples of the reductive ring opening of unactivated *cis*-aziridine-2-carboxylates with samarium diiodide (Table 3). The samarium diiodide used in these studies was prepared from samarium metal and methylene iodide, and no isomerization of the aziridine was observed. If the substituent in the 3-position is a phenyl group, then the only product that is observed is the C−C cleavage product. Yields in the range of 69−75% are observed for this product with N−H aziridines, as well as with benzhydryl substituents on the aziridine nitrogen (Table 3, entries 1 and 2). A complete switch in the product distribution is seen with *cis*-aziridines bearing a cyclohexyl group in the 3-position. Here the β-amino ester is generated to the exclusion of the C−C cleavage product; the yields, however, are quite low (Table 3, entries 3 and 4). These

Table 3. Reductive Opening of Unactivated *cis*-Aziridines[a]



entry	PG	aziridine	R	A/B[b]	% yield A[c]	% yield B[c]
1	H	*cis*-**27a**	phenyl	<1:99		75 (**31a**)
2	$CHPh_2$	*cis*-**29a**	phenyl	<1:99		69 (**33b**)
3	$CHPh_2$	*cis*-**29b**	cyclohexyl	>99:1[d]	22 (**30b**)	
4	$CHPh_2$	*cis*-**29b**	cyclohexyl	>99:1[e]	22 (**30b**)	

[a]Unless otherwise specified, all reactions used 0.2 mmol of aziridine in THF (0.07 M) with 5 equiv of SmI2 and 10 equiv of DMEA at 0 °C for 40 min and were allowed to go to completion. [b]Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c]Isolated yield after silica-gel chromatography. [d]Isolated as a 1:1.4 mixture of **30b** and *cis*-**29b** (22% + 31%). The ^{1}H NMR indicated the formation of amine **34** in 39% yield. [e]Reaction was run for 2 h at 25 °C. Amine **34** was isolated in 52% yield, and aziridine *cis*-**29b** was isolated in 20% yield.

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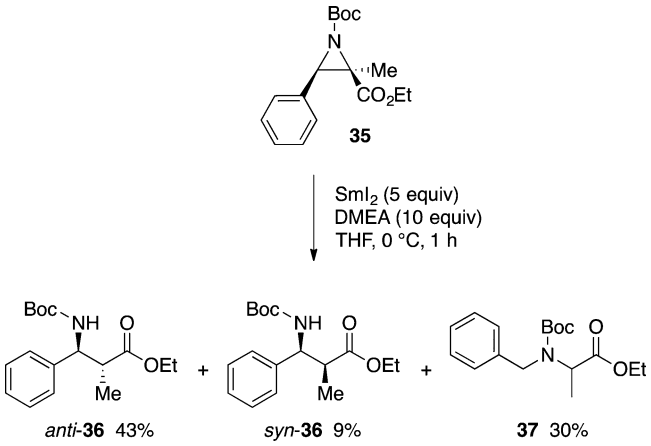
reactions produce a complex mixture from which only β-amino ester **30b**, starting *cis*-aziridine **29b**, and benzhydryl amine **34** could be isolated and characterized. The isolation of **34** suggests that β-cyclohexyl ethyl acrylate should also be formed, but it could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture.

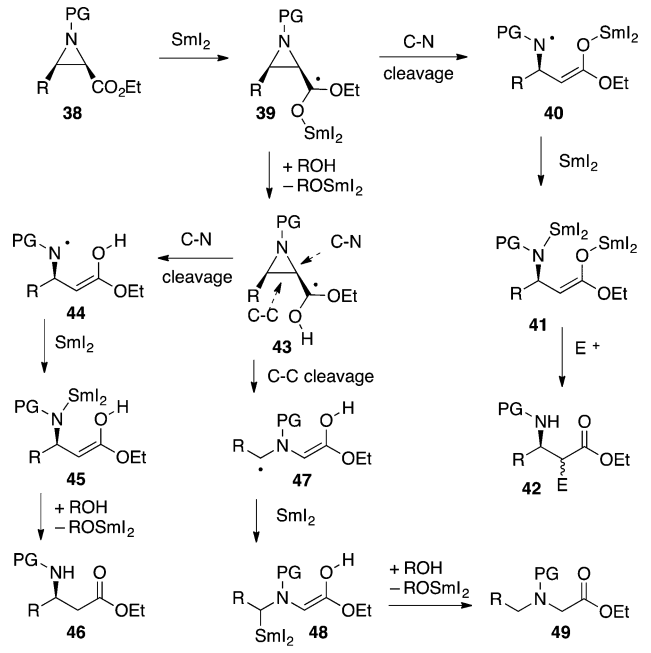
The reductive ring opening of stereoisomerically pure trisubstituted aziridine **35**[20] occurs with loss of stereochemical information and the formation of two diastereomers in a ratio of 4.8:1 (Scheme 4). The major diastereomer was identified as the

Scheme 4



anti isomer of **36** by chemical correlation to a known compound (Supporting Information). This loss of stereochemistry is to be expected on the basis of the likely mechanism for this reaction (Scheme 5). The ring opening of **35** also occurs with the formation of C−C cleavage product **37** in 30% yield. Note that the distribution between C−N and C−C cleavage products is essentially the same as for cis disubstituted *N*-Boc aziridine *cis*-**15a** (Table 2, entry 1).

Scheme 5



The generally accepted mechanism for the reductive ring opening of aziridines by samarium diiodide is illustrated in Scheme 5.[13b] After initial reduction to form ketyl **39** and in the absence of a proton source, this species then undergoes a ring opening to give nitrogen-based radical **40** that, upon further reduction, gives the species **41**, containing both a samarium enolate and a samarium amide. The intermediacy of this enolate has been demonstrated, and its utility has been displayed in its alkylation with alkyl halides[13b] and aldol reactions with aldehydes.[13c] Under conditions where a proton source is present, ketyl **39** is thought to be protonated to give neutral radical **43** that, depending on the nature of the aziridine, then undergoes a C−N and/or C−C bond scission. Subsequent reduction of the resulting nitrogen- or carbon-based radicals **44** and **47** and final protonation would provide β-amino ester **46** and/or glycine derivative **49**. This mechanistic interpretation accounts for the observations made in the present work. Of all of the examples in Tables 1 and 2, the aziridines with a cyclohexyl group in the 3-position give a much higher selectivity for the β-amino ester over the glycine derivative than do aziridines with a phenyl group in the 3-position. This reflects a higher preference for C−C over C−N cleavage for the phenyl aziridines than for the cyclohexyl aziridines, which can be attributed to the greater stability of a benzyl radical compared to an alkyl radical in intermediate **47**. Conversely, the presence of a radical stabilizing group on the nitrogen facilitates the ring opening with C−N bond scission over C−C bond scission. This can be seen in the ring-opening reactions of activated aziridines (Tables 1 and 2) versus unactivated aziridines (Table 3). This is illustrated by the comparison of *N*-tosyl aziridine *cis*-**16a** (Table 2, entry 5) to *N*-benzhydryl aziridine *cis*-**29a** (Table 3, entry 3) and by the comparison of *N*-tosyl aziridine *cis*-**16a** (Table 2, entry 5) to *N*-Boc aziridine *cis*-**15a** (Table 2, entry 1).

The ratio of C−N versus C−C cleavage is a function not only of the radical stabilizing ability of the substituent on the nitrogen and the substituent on the C-3 position of the aziridine but also of the stereochemistry of the aziridine. The *cis*-aziridines exhibit a much greater preference for C−C bond cleavage than do the *trans*-aziridines. *N*-Boc aziridine *trans*-**15a** gives a 6.7:1 mixture of C−N to C−C cleavage products, whereas the corresponding *cis*-**15a** gives a much greater propensity for the C−C cleavage product (1.4:1, Table 2, entries 1 and 3, respectively). The same is also true for *N*-Fmoc aziridines *cis*-**11a** and *trans*-**11a** (Table 1, entries 1 and 3, respectively). The greater preference for C−C cleavage products with *cis*-aziridines may be due to a relief in steric interactions between the two *cis*-substituents in the transition state, allowing the C−C bond to begin to lengthen (Scheme 6). It is intersting that this relief in steric interaction would not be realized in the *trans*-aziridine. C−C cleavage products have been rarely seen in the reductive ring opening of aziridines involving single electron-transfer processes; this may be due to the fact that *cis*-aziridines have not been previously evaluated in this reaction. The only example that we are aware of involves an unactivated (N−H) aziridine-2-carboxylate with a *trans*-phenyl group in the 3-position, which gives a 28:16 split between C−N and C−C cleavage products,[13b] as compared to aziridine *cis*-**27a**, which gives exclusively the C−C cleavage product in 75% yield (Table 3, entry 1). From the synthesis point of view, the N-tosyl group is the protecting group of choice for samarium diiodide-mediated reductive ring opening of aziridines if removal of the tosyl group does not cause problems in a later stage. *N*-Tosyl aziridines are completely selective for the C−N cleavage product (>99:1) for both the *cis*- and *trans*-aziridines,

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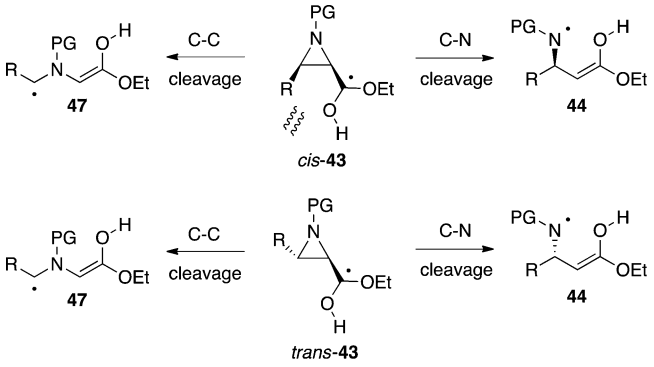
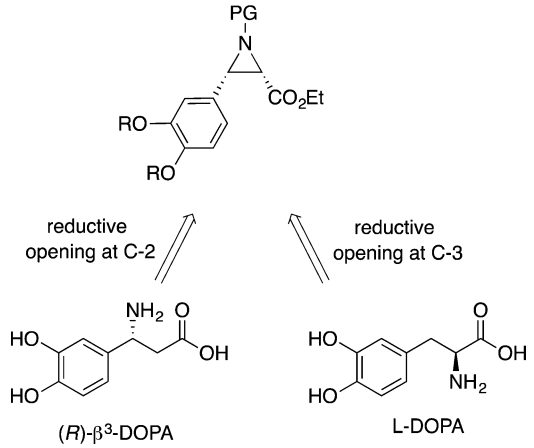
Scheme 6



with both aryl and alkyl substituents in the 3-position (Table 2, entries 5−8). The SES protecting group can be considered to be an alternative to a tosyl sulfonamide, which is notorious for its potential to be troublesome during deprotection. SES-protected aziridine *cis*-**17a** gave excellent selectivity (23:1, Table 2) for the β-amino ester, and the deprotection of SES is known to proceed under much milder reaction conditions.

The utility of aziridine-2-carboxylates in the preparation of both α- and β-amino acids is illustrated in Scheme 7, which shows

Scheme 7



how the same aziridine provides access to both L-DOPA and (*R*)-β^3-DOPA. L-DOPA is the biological precursor to the catecholamine neurotransmitters, a treatment of Parkinson's disease,[21] and a key compound in the formation of marine-adhesive proteins.[22] L-DOPA became the first commercial pharmaceutical agent to be manufactured by a nonproteinaceous asymmetric catalyst, which was acknowledged in the 2001 Nobel Prize in chemistry to William S. Knowles.[23] The isomeric (*R*)-β^3-DOPA has been isolated as an iron(III) complex from a dark-blue-violet mushroom of the species *Cortinarius violaceus*.[24,25] Both natural products could potentially be obtained from the reductive opening of the same aziridine via controlled reductive ring opening at the C-2 and C-3 positions. Of the many synthesis methods of L-DOPA and (*R*)-β^3-DOPA, no other method can provide access to both isomers from the same asymmetric strategy.[23−25,41]

Our first approach to the synthesis of L-DOPA and (*R*)-β^3-DOPA began with bis-acetoxy aziridine **54**, which was prepared in one step in 98% yield and >98.5% ee from aldehyde **50**, amine **52**, and ethyl diazoacetate **53** by a catalytic, asymmetric, multicomponent aziridination with 5 mol % VAPOL BOROX catalyst (Scheme 8).[5] To set the stage for the regiocomplementary reductive ring opening of aziridine **54**, the MEDAM group was cleaved with trifluoracetic acid in anisole and the resulting N−H aziridine was not purified but rather directly protected by TsCl or SESCl to give N-protected aziridines **57** and **58** in 70 and 78% yield, respectively, for the two steps. The samarium diiodide-mediated ring opening of both tosyl aziridine **57** and SES-aziridine **58** gave complex mixtures because of the cleavage of zero, one, or two of the acetoxy groups on the benzene ring. By treating the crude mixtures with acetic anhydride in the presence of triethylamine, β-amino esters **61A** and **62A** were isolated in good yields, although an increase in the yield of the C−C cleavage product was observed in both cases compared to the corresponding phenyl-substituted aziridines *cis*-**16a** and *cis*-**17a** (Table 2). This may be due to the electronic effect of the two acetate groups on the benzene ring. Despite the effort that was expended to investigate the removal of the tosyl group following many of the standard procedures, **61A** could not be deprotected without decomposition.

Before exploring of SES-deprotection of **62A**, we turned our attention to the acetate cleavage problem in the samarium diiodide ring-opening process. This was solved by replacing the acetate groups with the bulky *tert*-butyl acyloxy (pivaloyl) groups. The catalytic asymmetric multicomponent aziridination worked smoothly with aldehyde **51** and afforded aziridine **55** in 97% yield and 98% ee. Interestingly, the MEDAM group could be removed with trifluoroacetic acid in anisole without the cleavage of the pivaloyl groups and then directly reacting the N−H aziridine with SESCl gave aziridine **59** in 86% yield. The formation of β-amino ester **63A** was smoothly achieved (74% yield) from the reductive ring-opening reaction with no detection of cleavage of the pivolyl groups. The first attempt to remove the SES group from the amine function in **63A** following a literature procedure[19] involving heating with CsF in DMF at 95 °C resulted in the formation of only ethyl 3,4-dihydroxycinnamate **65** in 65% yield (NMR yield). This is probably due to fluoride-mediated deprotonation at the α-position of the carbonyl, causing an elimination of the SES-amino group. Alternatively, **65** could result from a fluoride-mediated cleavage of the pivaloyl group, followed by a phenoxide-assisted elimination of the SES-amino group and a final rearomatization. A similar outcome was also observed for SES-protected β-amino ester **62A**. It has been previously reported that the elimination of the SES group from SES-protected α-amino carbonyl compounds can be a problem during the SES deprotection step.[26] However, there is no example reported for the elimination of the SES-NH_2 group from a β-amino ester during SES deprotection. It is known that N-acyl-substituted SES groups are much more readily deprotected than simple SES groups.[26] On the basis of the latter, we carried out the acylation of **63A** by treating it with $(Boc)_2O$ and subsequently treating the crude mixture with TBAF in THF at 25 °C for 1.5 h to afford the desired β-amino ester **64**, the protected form of (*R*)-β^3-DOPA, in 88% isolated yield. There was some cleavage of the pivaloyl groups by TBAF, and thus a workup with pivaloyl chloride gives **64** as a pure compound. No purification was performed during any of the steps in the conversion of **63A** to **64**. Finally, the reductive ring opening of aziridine **55** with palladium hydroxide-catalyzed hydrogenation in the presence of $(Boc)_2O$ resulted in the formation of α-amino ester **56**, the protected form of L-DOPA, in 86% isolated yield.

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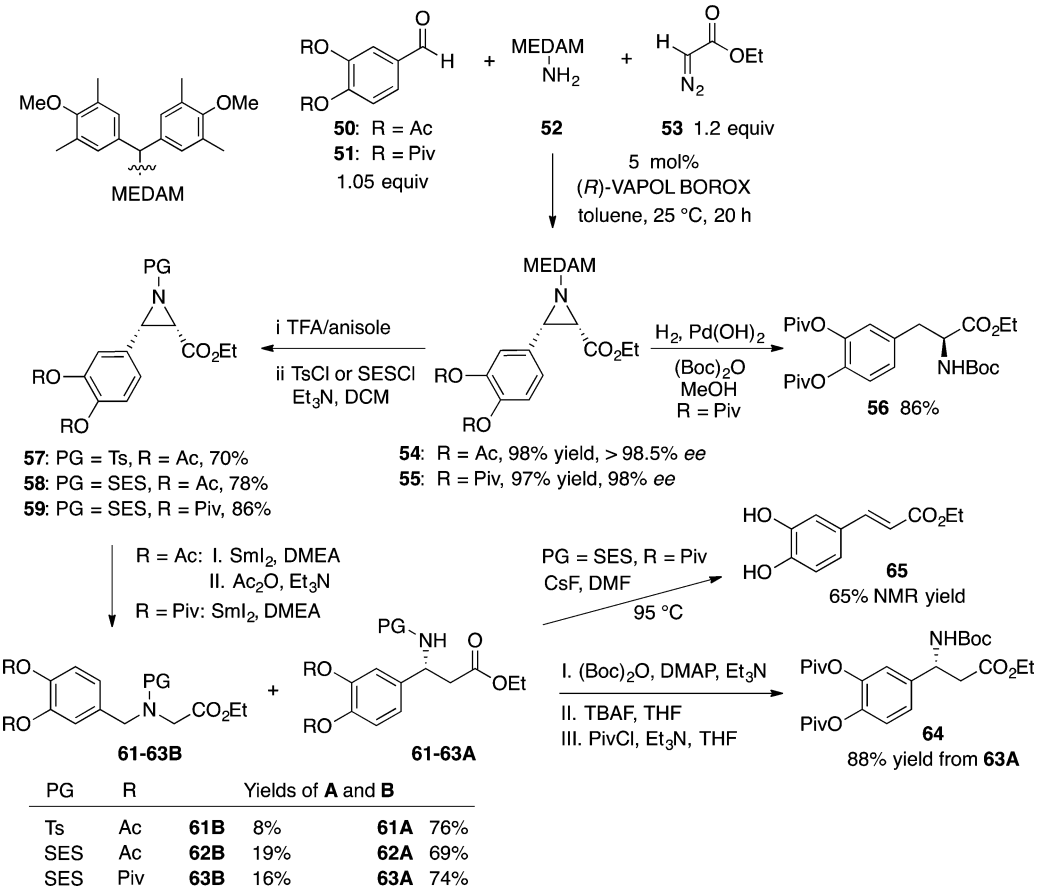
Scheme 8



PG	R	Yields of **A** and **B**			
Ts	Ac	**61B**	8%	**61A**	76%
SES	Ac	**62B**	19%	**62A**	69%
SES	Piv	**63B**	16%	**63A**	74%

3. CONCLUSIONS

The reductive ring opening of 3-substituted aziridine-2-carboxylates with samarium diiodide can be controlled to proceed via C−N bond cleavage to give high yields of *β*-amino esters. The competing C−C bond cleavage gives rise to glycine derivatives. It is necessary to have an activating group on the aziridine nitrogen to achieve selective C−N bond cleavage. Aziridines with nonactivating nitrogen substituents (hydrogen or benzhydryl) exclusively form glycine derivatives when there is a phenyl group in the 3-position and, when there is a cyclohexyl group in the 3-position, low yields of *β*-amino esters and other decomposition products. The selectivity between C−N and C−C bond cleavage directly correlates with the electron-withdrawing power of the activating group on the nitrogen. Sulfonyl groups give higher selectivity than carbamate groups, and this is especially noticeable with *cis*-aziridines that have a phenyl group in the 3-position. The lower selectivity with *cis*-aziridines is thought to be due to a steric release during the C−C bond cleavage, leading to glycine products. The utility of this methodology is illustrated in the synthesis of a protected form of (*R*)-β^3-DOPA by the reductive opening of aziridine **59** with samarium diiodide to give *β*-amino ester **63A**. Furthermore, this synthesis features the targeting of (*R*)-β^3-DOPA and its regioisomer L-DOPA by ring opening of the same aziridine, **55**, the former by reductive opening at the C-2 position and the latter by reductive opening at the C-3 position.

4. EXPERIMENTAL SECTION

Tetrahydrofuran (THF) and toluene were distilled from sodium under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Other reagents were used as purchased. VAPOL was prepared according to literature procedures and was determined to be at least 99% optically pure.[27] The preparation of aziridine esters *cis*-**11a,b**,[18] *cis*-**15a,b**,[18] *cis*-**16a,b**,[18] *cis*-**27a**,[18] *trans*-**27a**,[28] *cis*-**29a,b**,[7a] and **35**[20] has been previously reported.

Melting points were determined on a capillary melting-point apparatus and were uncorrected. IR spectra were taken on an FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300, 500, or 600 MHz spectrometer in $CDCl_3$, unless otherwise noted. $CHCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.24) and ^{13}C NMR (δ = 77.0). HR-MS was performed on a TOF-MS spectrometer. Analytical thin-layer chromatography (TLC) was performed on silica-gel plates with an F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, by staining with phosphomolybdic acid in ethanol, or with the aid of iodine vapor. Column chromatography was performed with silica gel 60 (230−450 mesh). Optical rotations were obtained on a polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C.

4.1. *trans*-*N*-9-Fluorenylmethyl-carbamate-2-carboxyethyl-3-phenylaziridine (11a). To a 100 mL round-bottomed flask were added racemic *trans*-2-carboxyethyl-3-phenylaziridine **27a** (0.296 g, 1.5 mmol, 1.0 equiv), $NaHCO_3$ (0.252 g, 3.0 mmol, 2.0 equiv), 30 mL of a mixture of acetone, and H_2O (3:1). The mixture was stirred at room temperature for 5 min, and then 9-fluorenylmethylchloroformate (0.388 g, 1.5 mmol, 1.0 equiv) was added. The reaction mixture was then stirred at room temperature for 48 h. The acetone was removed by rotary evaporation, and the aqueous residue was extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with sat aq NaCl, dried over $MgSO_4$, and concentrated by rotary evaporation to afford a yellow oil. Purification by silica-gel chromatography (column 1: 18 mm

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× 250 mm, 4:1:1 hexanes/diethyl ether/CH_2Cl_2 as eluent; column 2: 18 mm × 250 mm, CH_2Cl_2 as eluent) afforded *trans*-**11a** as a colorless oil in 72% isolated yield that solidified upon standing (white solid, mp 93−95 °C). Spectral data for *trans*-**11a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz), 3.20 (d, 1H, J = 2.4 Hz), 3.90 (d, 1H, J = 2.4 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.24 (t, 1H, J = 7.2 Hz), 4.33 (dd, 1H, J = 10.5, 7.8 Hz), 4.48 (dd, 1H, J = 10.5, 7.2 Hz), 7.25−7.31 (m, 2H), 7.32−7.42 (m, 7H), 7.55−7.61 (m, 2H), 7.74 (d, 2H, J = 7.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 44.2, 45.1, 46.8, 62.2, 68.8, 119.96, 119.97, 125.2, 125.3, 126.4, 127.05, 127.06, 127.7, 127.8, 128.6, 128.7, 134.9, 141.25, 141.26, 143.6, 143.7, 159.7, 167.3; IR (thin film) 1744 (vs), 1179 (s) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{26}H_{24}NO_4^+$, 414.1705; found, 414.1731.

4.2. *trans*-*N*-9-Fluorenylmethyl-carbamate-*cis*-2-carboxyethyl-3-cyclohexylaziridine (11b). The aridizine was prepared according to the procedure described above for *trans*-**11a** starting with racemic *trans*-2-carboxyethyl-3-cyclohexylaziridine[29] (296 mg, 1.50 mmol). Purification by silica-gel chromatography (15 mm × 250 mm, 8:1 hexanes/EtOAc as eluent) afforded *trans*-**11b** as a colorless oil in 91% isolated yield (572 mg, 1.36 mmol). Spectral data for *trans*-**11b**: R_f = 0.28 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16−1.28 (m, 6H), 1.22 (t, 3H, J = 7.2 Hz), 1.62−1.68 (m, 1H), 1.69−1.78 (m, 3H), 1.81 (d, 1H, J = 12 Hz), 2.66 (dd, 1H, J = 7.2, 2.7 Hz), 2.96 (d, 1H, J = 2.7 Hz), 4.08−4.16 (m, 2H), 4.22 (t, 1H, J = 6.9 Hz), 4.32 (dd, 1H, J = 10.5, 7.5 Hz), 4.46 (dd, 1H, J = 10.2, 7.2 Hz), 7.27−7.31 (m, 2H), 7.38 (t, 2H, J = 7.5 Hz), 7.60 (t, 2H, 1H, J = 7.8 Hz), 7.74 (d, 2H, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 25.5, 25.6, 26.0, 29.7, 29.9, 39.2, 39.4, 46.9, 49.0, 61.8, 68.3, 119.90, 119.91, 125.1, 125.2, 127.01, 127.03, 127.66, 127.70, 141.27, 141.29, 143.7, 143.8, 160.2, 168.3; IR (thin film) 2928 (s), 2853 (w), 1743 (vs), 1451 (m), 1310 (m), 1177 (s) cm^{-1}; mass spectrum, m/z (% rel intensity) 419 M$^+$ (0.07), 346 (0.15), 178 (100), 165 (62), 84 (34), 49 (56); HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{26}H_{30}NO_4^+$, 420.217; found, 420.216.

4.3. *trans*-*N*-Boc-2-carboxyethyl-3-phenylaziridine (15a). To a flame-dried 25 mL round-bottomed flask filled with argon were added *trans*-2-carboxyethyl-3-phenylaziridine **27a**[28] (150 mg, 0.784 mmol) and 5 mL of MeOH followed by the addition of $NaHCO_3$ (197 mg, 0.450 mmol, 3.00 equiv). The flask was put in an ultrasonic bath for 5 min, and then $(Boc)_2O$ (428 mg, 1.96 mmol, 2.50 equiv) was added. The mixture was left in the ultrasonic bath for 4 h with a needle in the rubber septum to release the generated CO_2 gas. After 4 h, additional portions of both $NaHCO_3$ and $(Boc)_2O$ in equal amounts were added. The reaction mixture was then stirred for 4 days. The reaction mixture was filtered through Celite, and the solid residue was washed with Et_2O. The cloudy filtrate was filtered again through Celite, and then concentrated by rotary evaporation to afford the crude product as a colorless liquid. Purification by silica-gel chromatography (15 mm × 250 mm, hexanes and then 1:9 ethyl acetate/hexanes as eluent) afforded *trans*-**15a** as a colorless oil in 71% isolated yield (163 mg, 0.56 mmol). Spectral data for *trans*-**15a**: R_f = 0.36 (hexanes/EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz), 1.44 (s, 9H), 3.07 (d, 1H, J = 2.6 Hz), 3.79 (d, 1H, J = 2.6 Hz), 4.14−4.36 (m, 2H), 7.24−7.36 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.16, 27.88, 44.02, 44.92, 61.82, 82.04, 126.43, 128.27, 128.48, 135.33, 158.29, 167.40. The ^{1}H and ^{13}C NMR data match those previously reported for this compound.[13b]

4.4. *trans*-*N*-Boc-2-carboxyethyl-3-cyclohexylaziridine (15b). To a flame-dried 25 mL round-bottomed flask filled with argon were added racemic *trans*-2-carboxyethyl-3-cyclohexylaziridine[29] (198 mg, 1.0 mmol, 1.0 equiv), MeOH (6.5 mL), and $NaHCO_3$ (0.84 g, 10 mmol, 10 equiv). The flask was put in an ultrasonic bath for 5 min, and then $(Boc)_2O$ (1.09 g, 5.00 mmol, 5.00 equiv) was added. The mixture was left in the ultrasonic bath for 4 h with a needle in the rubber septum to release the generated CO_2 gas, and then it was stirred at room temperature for another 18 h. The reaction mixture was filtered through Celite, and the filter cake was washed with diethyl ether. The cloudy filtrate was filtered again through Celite and then concentrated by rotary evaporation to afford the crude product as a light-yellow liquid. Purification by silica-gel chromatography (15 mm × 250 mm, 45:1 hexanes/EtOAc as eluent until the first fraction came out and then 15:1 hexanes/EtOAc as eluent) afforded *trans*-**15b** as a colorless oil in 89% isolated yield (265 mg, 0.89 mmol). Spectral data for *trans*-**15b**: R_f = 0.42 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04−1.25 (m, 6H), 1.28 (t, 3H, J = 7.2 Hz), 1.43 (s, 9H), 1.60−1.65 (m, 1H), 1.66−1.76 (m, 3H), 1.80−1.86 (m, 1H), 2.60 (dd, 1H, J = 6.8, 3.0 Hz), 2.83 (d, 1H, J = 3.0 Hz), 4.11−4.28 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 25.5, 25.6, 26.1, 28.0, 29.7, 30.0, 39.3, 39.4, 48.7, 61.5, 81.5, 159.0, 168.4; IR (thin film) 2980 (w), 2930 (s), 2855 (w), 1744 (vs), 1728 (s), 1154 (s) cm^{-1}; mass spectrum, m/z (% rel intensity) 224 (M$^+$ − 73) (5.6), 196 (21), 124 (85), 95 (73), 57 (100); Anal. calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.88; H, 9.27; N, 4.72.

4.5. *trans*-*N*-Tosyl-2-ethoxycarbonyl-3-phenylaziridine (*trans*-16a). To a flame-dried 50 mL round-bottomed flask filled with argon were added racemic *trans*-2-carboxyethyl-3-phenylaziridine **27a**[28] (0.335g, 1.75 mmol, 1.0 equiv) and CH_2Cl_2 (14 mL, freshly distilled). The solution was cooled to 0 °C in an ice bath followed by the addition of Et_3N (0.7 mL, 5.03 mmol, 2.9 equiv, freshly distilled). After the reaction mixture was stirred for 5 min at 0 °C, TsCl (0.534 g, 2.8 mmol, 1.6 equiv) was added to the mixture at 0 °C. Thereafter, the ice bath was removed and the mixture was stirred at room temperature for 94 h. The reaction was quenched by the addition of 26 mL of sat aq NH_4Cl and 5 mL of H_2O. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was washed with the following reagents in the indicated sequence: 5 mL of H_2O, 10 mL of aq citric acid, 5 mL of H_2O, 10 mL of sat aq $NaHCO_3$, and 20 mL of sat aq NaCl. The combined organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation to afford the crude product as an orange oil. Purification by silica-gel chromatography (column 1: 15 mm × 250 mm, 40:9 hexanes/EtOAc as eluent; column 2: 15 mm × 250 mm, 16:4:1 hexanes/CH_2Cl_2/EtOAc as eluent) afforded *trans*-**16a** as a light-yellowish oil in 54% yield (0.326 g, 0.94 mmol). Spectral data for *trans*-**16a**: R_f = 0.24 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7.0 Hz), 2.39 (s, 3H), 3.49 (d, 1H, J = 3.9 Hz), 4.20−4.39 (m, 2H), 4.41 (d, 1H, J = 3.9 Hz), 7.19−7.31 (m, 7H), 7.71−7.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 21.6, 47.1, 47.7, 62.4, 127.3, 127.5, 128.6, 128.9, 129.5, 132.7, 137.2, 144.2, 165.7. The ^{1}H and ^{13}C NMR data match those previously reported for this compound.[13b]

4.6. *trans*-*N*-Tosyl-2-ethoxycarbonyl-3-cyclohexylaziridine (16b). According to the same procedure used for *trans*-**16a**, racemic *trans*-2-carboxyethyl-3-cyclohexylaziridine[29] (197 mg, 1.0 mmol, 1.0 equiv) was reacted with tosyl chloride (0.305 g, 1.6 mmol, 1.6 equiv) and Et_3N (freshly distilled, 0.42 mL, 3.0 mmol, 3.0 equiv) in 1:1(v/v) $CH_2Cl_2/CHCl_3$ (8 mL) for 72 h. Purification by silica-gel chromatography (column 1: 15 mm × 250 mm, 10:1 hexanes/EtOAc; column 2: 15 mm × 250 mm, 6:1:16 CH_2Cl_2/diethyl ether/hexanes as eluent) and recrystallization from hexanes afforded *trans*-**16b** as white crystals (mp 71−73 °C) in 70% isolated yield (246 mg, 0.70 mmol). Spectral data for *trans*-**16b**: R_f = 0.26 (5:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00−1.35 (m, 8H), 1.58−1.79 (m, 5H), 1.95 (d, 1H, J = 10.5 Hz), 2.41 (s, 3H), 3.02 (dd, 1H, J = 9.0, 4.2 Hz), 3.18 (d, 1H, J = 4.2 Hz), 4.15 (q, 2H, J = 6.9 Hz), 7.24−7.32 (m, 2H), 7.79−7.83 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 21.6, 25.2, 25.4, 25.9, 30.6, 31.1, 37.5, 43.7, 53.7, 61.9, 127.5, 129.5, 137.1, 144.2, 166.7; IR (thin film) 2930 (s), 2855 (m), 1745 (s), 1331 (s), 1101 (s) cm^{-1}; mass spectrum, m/z (% rel intensity) 306 (M$^+$ − 45) (2.3), 278 (3.2), 197 (34), 196 (100), 168 (29), 122 (88), 67 (83); Anal. calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. found: C, 61.60; H, 7.22; N, 3.96.[30]

4.7. *cis*-Ethyl-(2*R*,3*R*)-3-phenyl-1-((2-(trimethylsilyl)ethyl)-sulfonyl)aziridine-2-carboxylate (17a). To a flame-dried 10 mL round-bottomed flask were added 2-(trimethylsilyl)ethanesulfonyl chloride (82.5 μL, 0.639 mmol, 1.28 equiv), Et_3N (0.7 mL, 5 mmol, 10 equiv), and CH_2Cl_2 (2 mL, freshly distilled). The mixture was precooled in an ice bath for 5 min. *cis*-(2*R*,3*R*)-2-Carboxyethyl-3-phenylaziridine **27a**[18] (95.6 mg, 0.5 mmol, 1 equiv, 98% ee) was dissolved in 0.5 mL of CH_2Cl_2, and the solution was added dropwise to the 10 mL round-bottomed flask containing 2-(trimethylsilyl)-ethanesulfonyl chloride. The ice bath was removed, and the reaction mixture was stirred at room temperature for 45 h. Subsequently, additional portions of 2-(trimethylsilyl)ethanesulfonyl chloride (160 μL, 1.26 mmol, 2.5 equiv) and Et_3N (0.7 mL, 5 mmol, 10 equiv) were

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added to the reaction mixture. After the mixture was stirred for 24 h at room temperature, the reaction was quenched with 2 mL of sat aq NH_4Cl and 1 mL of H_2O. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated to give a dark-brown oil. Purification by silica-gel chromatography (15 mm × 180 mm, 9:1 hexanes/EtOAc as eluent) afforded *cis*-**17a** as a light-yellow oil in 83% yield (0.147 g, 0.413 mmol). Spectral data for *cis*-**17a**: R_f = 0.19 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.00 (t, 3H, J = 7.0 Hz), 1.13−1.24 (m, 2H), 3.16−3.26 (m, 2H), 3.67 (d, 1H, J = 7.5 Hz), 3.93−4.05 (m, 2H), 4.07 (d, 1H, J = 7.5 Hz), 7.26−7.34 (m, 3H), 7.37−7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.0, 9.7, 13.9, 43.7, 44.3, 49.5, 61.6, 127.5, 128.3, 128.7, 131.4, 164.5; IR (thin film) 2955 (s), 1755 (vs) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{26}NO_4SSi^+$, 356.1352; found, 356.1351; $[\alpha]_D^{20}$ = −38.0° (c 1.0, CH_2Cl_2) on 98% ee material (the optical purity was assumed to be unchanged from **27a**).

4.8. *cis*-(2*R*,3*R*)-Ethyl-1-acetyl-3-phenylaziridine-2-carboxylate (18a). To a 25 mL flame-dried round-bottomed flask filled with argon were added *cis*-(2*R*,3*R*)-2-carboxyethyl-3-phenylaziridine **27a**[18] (38 mg, 0.20 mmol), 1 mL $CHCl_3$, Et_3N (90 μL, 0.65 mmol), and acetic anhydride (29 μL, 0.31 mmol) at room temperature. The mixture was stirred at room temperature for 4 h, and then the solvent was removed under reduced pressure to give the crude *cis*-(2*R*,3*R*)-**18a** product as a white solid. Purification by silica-gel chromatography (9 mm × 250 mm, 1:5 EtOAc/hexanes as eluent) gave **18a** as a white solid in 100% yield (47 mg, 0.20 mmol). Spectral data for *cis*-(2*R*,3*R*)-**18a**: R_f = 0.35 (1:5, EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.1 Hz), 2.20 (s, 3H), 3.47 (d, 1H, J = 6.6 Hz), 3.81 (d, 1H, J = 6.6 Hz), 3.85−3.97 (m, 2H), 7.24−7.31 (m, 3H), 7.35−7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 23.1, 42.0, 43.5, 61.1, 127.3, 128.0, 128.2, 132.5, 165.6, 181.13; IR (thin film) 1747 (s), 1713 (s) cm^{-1}; mass spectrum, m/z (% rel intensity) 233 M^+ (0.09), 191 (14), 146 (11), 117 (100), 91 (18), 79 (10), 55 (12), 43 (44). Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.87; H, 6.85; N, 5.94.

4.9. Representative Procedure for the Reductive Ring Opening of Aziridine-2-carboxylates with SmI_2 (Illustrated for *cis*-15a). To a flame-dried 10 mL round-bottomed flask filled with argon were added Sm (180 mg, 1.20 mmol, 6.00 equiv) and dry THF (1.8 mL, freshly distilled). The vacuum adapter on the flask was changed to a rubber septum, and the suspension was purged with nitrogen under the surface of the solution for 5 min by a needle through the septum. Another needle in the septum was used as an outlet for the nitrogen gas. CH_2I_2 (92.5 μL, 1.15 mmol, 5.7 equiv) was then added to the reaction flask, and the reaction mixture was purged with nitrogen for another 1 min. The outlet needle was removed, and the needle used for nitrogen flow was lifted above the surface of the solution. The reaction mixture was stirred at room temperature for 2 h, resulting in a dark-blue slurry. The slurry was then precooled to 0 °C in an ice bath. Subsequently, to a flame-dried 5 mL round-bottomed flask filled with nitrogen were added *cis*-(2*R*,3*R*)-**15a**[18] (78% ee, 60 mg, 0.2 mmol, 1.0 equiv), dry THF (1.5 mL, freshly distilled), and *N*,*N*-dimethylethanolamine (0.24 mL, 2.4 mmol, 12.0 equiv). The solution was purged with nitrogen under the surface of the solution for 2 min and transferred to the flask containing the SmI_2 slurry dropwise via cannula. Vigorous stirring was maintained during the addition of the aziridine to the SmI_2 slurry. The 5 mL flask was washed with 0.3 mL of degassed THF, and the rinse was also transferred to the reaction flask containing SmI_2. The reaction mixture was stirred at 0 °C for 40 min to 1 h and then quenched by the addition of sat aq $NaHCO_3$ (5 mL) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL × 4). The combined organic layer was dried with Na_2SO_4 and filtered. The solvent was removed by rotary evaporation to give a light-yellow solid. The ^{1}H NMR spectrum of the crude reaction mixture showed that it was a mixture of **19a** and **23a** in a ratio of 1.4:1. Purification by silica-gel chromatography (18 × 250 mm, 1:1:4.6 diethyl ether/hexanes/CH_2Cl_2 as eluent) afforded (*S*)-**19a** as a white solid (mp 75−77 °C) in 55% isolated yield (33.6 mg, 0.11 mmol) and **23a** as a colorless oil in 32% isolated yield (19.2 mg, 0.065 mmol). The optical purity of (*S*)-**19a** was determined to be 78% *ee* by HPLC analysis (Chiralcel OD-H column, 98:2 hexanes/iPrOH at 222 nm, flow rate: 1.0 mL/min); retention times of R_t = 6.24 min (minor enantiomer (*R*)-**19a**) and R_t = 7.08 min (major enantiomer (*S*)-**19a**). TLC and spectral data for (*S*)-**19a**: R_f = 0.24 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, 3H, J = 7.1 Hz), 1.40 (s, 9H), 2.70−2.90 (m, 2H), 4.05 (q, 2H, J = 7.1 Hz), 5.09 (brs, 1H), 5.46 (brs, 1H), 7.19−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.0, 28.3, 41.0, 51.2, 60.6, 79.6, 126.1, 127.4, 128.6, 141.2, 155.0, 170.88; $[\alpha]_D^{20}$ = −31.6 (c 1.0, EtOAc) on 78% *ee* (*S*)-**19a**.[31] TLC and spectral data for **23a** (mixture of rotamers): R_f = 0.34 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.219 and 1.224 (2t, 3H, J = 7.1 Hz), 1.447 and 1.452 (2s, 9H), 3.75 and 3.89 (2s, 2H), 4.13 and 4.14 (2q, 2H, J = 7.1 Hz), 4.49 and 4.52 (2s, 2H), 7.18−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 14.2, 28.2, 28.3, 47.7, 48.1 51.0, 51.5, 60.9, 61.0, 80.4, 80.6, 127.37, 127.43, 127.5, 128.1, 128.5, 137.4, 137.6, 155.6, 155.8, 169.90, 169.94.[32]

4.9.1. Reductive Ring Opening of trans-11a. The reaction was carried out according to the general procedure described above, starting with racemic *trans*-**11a** (62.1 mg, 0.15 mmol, 1.0 equiv), SmI_2 (5.5 equiv), *N*,*N*-dimethylethanolamine (0.17 mL, 1.7 mmol, 11.0 equiv), and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) held at 0 °C for 1 h. The ^{1}H NMR spectrum of the crude reaction mixture showed that **12a**[18] and **13a**[18] were obtained in a ratio of 16.7:1. The NMR yield of **12a** was determined to be 82% with the aid of Ph_3CH as an internal standard.

4.9.2. Reductive Ring Opening of trans-11b. This reaction was carried out according to the general procedure described above, starting with racemic *trans*-**11b** (62.7 mg, 0.15 mmol, 1.0 equiv), SmI_2 (6.0 equiv), *N*,*N*-dimethylethanolamine (0.18 mL, 1.8 mmol, 12.0 equiv), and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) held at 0 °C for 1 h. The NMR yield of **12b**[18] was determined to be 73% with the aid of Ph_3CH as an internal standard.

4.9.3. Reductive Ring Opening of trans-15a. The reaction was carried out according to the general procedure described above, starting with racemic *trans*-**15a** (58.3 mg, 0.2 mmol, 1.0 equiv), SmI_2 (6.0 equiv), *N*,*N*-dimethylethanolamine (0.24 mL, 2.4 mmol, 12.0 equiv), and dry THF (1.8 mL for SmI_2 and 1.8 mL for aziridine, freshly distilled) held at 0 °C for 1 h. The ^{1}H NMR spectrum of the crude reaction mixture showed that **19a** and **23a** were present in a ratio of 6.7:1. Purification by silica-gel chromatography (18 × 250 mm, 1:1:4.6 diethyl ether/hexanes/CH_2Cl_2 as eluent) afforded **19a** as a white solid (mp 75−77 °C) in 85% isolated yield (50.1 mg, 0.17 mmol) and **23a** as a colorless oil in 10% isolated yield (5.9 mg, 0.02 mmol). The spectral data for **19a** and **23a** are the same as those obtained in the reductive ring opening of *cis*-**15a**.

4.9.4. Reductive Ring Opening of cis-15b. The general procedure for the reductive ring opening described above was followed, starting with *cis*-**15b**, except that 4 equiv of SmI_2 and 8 equiv of DMEA were used. Starting from *cis*-**15b**[18] (38 mg, 0.12 mmol), purification by silica-gel chromatography (18 mm × 150 mm, 1:5 EtOAc/hexanes as eluent) gave **19b** as a white solid in 84% isolated yield (30 mg, 0.1 mmol). The ^{1}H NMR spectrum of the crude reaction mixture showed the ratio of **19b**/**23b** > 99:1. TLC and spectral data for **19b**: R_f = 0.25 (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83−0.99 (m, 2H), 1.01−1.17 (m, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.38 (s, 9H), 1.31−1.40 (m, 1H), 1.61−1.75 (m, 5H), 2.38−2.51 (m, 2H), 3.63−3.75 (m, 1H), 4.08 (q, 2H, J = 7.1 Hz), 4.88 (d, 1H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 25.98, 26.02, 26.2, 28.3, 28.9, 29.7, 37.0, 41.5, 52.2, 60.4, 79.0, 155.5, 172.0; IR (thin film) 3360 (br, s), 2930 (s), 1719 (vs), 1504 (m), 1173 (s) cm^{-1}. The ^{1}H NMR spectral data match those previously reported for this compound.[33] The spectral data for **23b** has been reported.[34]

4.9.5. Reductive Ring Opening of trans-15b. The reaction was carried out according to the general procedure described above, starting with racemic *trans*-**15b** (59.5 mg, 0.2 mmol, 1.0 equiv), SmI_2 (6.0 equiv), *N*,*N*-dimethylethanolamine (0.24 mL, 2.4 mmol, 12.0 equiv), and dry THF (1.8 mL for SmI_2 and 1.8 mL for aziridine, freshly distilled) held at 0 °C for 1 h. β-Amino ester **19b** was obtained in 84% NMR yield with the aid of Ph_3CH as an internal standard. The ^{1}H NMR spectrum of the crude reaction mixture showed the ratio of **19b**/**23b** > 99:1.

*4.9.6. Reductive Ring Opening of trans-**16a**.* The reaction was carried out according to the general procedure described above, starting with racemic *trans*-**16a** (51.9 mg, 0.15 mmol, 1.0 equiv), SmI_2 (6.0 equiv), *N*,*N*-dimethylethanolamine (0.18 mL, 1.8 mmol, 12.0 equiv), and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) held at 0 °C for 1 h. Purification by silica-gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded **20a** as a colorless liquid in 88% isolated yield (45.9 mg, 0.132 mmol). Spectral data for **20a**: R_f = 0.25 (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (t, 3H, J = 7.2 Hz), 2.35 (s, 3H), 2.72 (dd, 1H, J = 16, 6.0 Hz), 2.81 (dd, 1H, J = 16, 6.0 Hz), 3.94−4.05 (m, 2H), 4.70 (q, 1H, J = 6.7 Hz), 5.67 (d, 1H, J = 7.5 Hz), 7.06−7.11 (m, 2H), 7.12−7.19 (m, 5H), 7.56−7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 21.4, 41.2, 54.3, 60.9, 126.4, 127.1, 127.7, 128.5, 129.4, 137.5, 139.3, 143.2, 170.6. These data match those previously reported for this compound.[13b] The ^{1}H NMR spectrum of the crude reaction mixture showed the ratio of **20a**/**24a** > 99:1.

*4.9.7. Reductive Ring Opening of cis-**16b**.* The general procedure for the reductive ring opening described above was followed, starting with aziridine (2*R*,3*R*)-**16b**[18] (82% *ee*, 53.4 mg, 0.15 mmol, 1.0 equiv), SmI_2 (5.0 equiv), *N*,*N*-dimethylethanolamine (0.15 mL, 1.5 mmol, 10.0 equiv), and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) held at 0 °C for 1 h. Purification by silica-gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded (*S*)-**20b** as a colorless oil in 97% isolated yield (52.1 mg, 0.147 mmol). The optical purity of (*S*)-**20b** was determined to be 84% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexanes/iPrOH at 222 nm, flow rate: 1.0 mL/min); retention times: R_t = 12.73 min (major enantiomer (*S*)-**20b**) and R_t = 16.94 min (minor enantiomer (*R*)-**20b**). The ^{1}H NMR spectrum of the crude reaction mixture showed the ratio of **20b**/**24b** > 99:1. Spectral data for (*S*)-**20b**: R_f = 0.17 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.78 (qd, 1H, J = 12.0, 3.2 Hz), 0.87 (qd, 1H, J = 12.0, 3.2), 1.00−1.17 (m, 3H), 1.18 (t, 3H, J = 7.1 Hz), 1.37−1.45 (m, 1H), 1.54−1.61 (m, 2H), 1.63−1.70 (m, 2H), 1.73−1.81 (m, 1H), 2.25 (dd, 1H, J = 16.0, 5.6 Hz), 2.37 (dd, 1H, J = 16.0, 5.6 Hz), 2.39 (s, 3H), 3.26−3.34 (m, 1H), 4.01 (m, 2H), 5.24 (d, 1H, J = 9.3 Hz), 7.26 (d, 2H, J = 8.1 Hz), 7.72 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 21.5, 25.87, 25.93, 26.1, 29.1, 29.3, 35.9, 41.2, 55.5, 60.6, 127.0, 129.6, 138.2, 143.2, 171.6; IR (thin film) 3292 (m), 2928 (vs), 2854 (m), 1734 (vs), 1718 (s), 1456 (m), 1324 (s), 1161 (vs) cm^{-1}; mass spectrum, m/z (% rel intensity) 354 (MH^+) (6.4), 271 (31), 270 (100), 224 (50), 198 (42), 155 (86), 91 (86), 41 (12); Anal. calcd for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.70; N, 3.96. Found: C, 61.30; H, 8.12; N, 3.88. $[\alpha]_D^{20}$ = −10 (c 0.4, EtOAc) on 84% ee (*S*)-**20b**.[35]

*4.9.8. Reductive Ring Opening of trans-**16b**.* The reaction was carried out according to the general procedure described above, starting with racemic *trans*-**16b** (53.3 mg, 0.15 mmol, 1.0 equiv), SmI_2 (6.0 equiv), *N*,*N*-dimethylethanolamine (0.18 mL, 1.8 mmol, 12.0 equiv), and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) held at 0 °C for 1 h. Purification by silica-gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded **20b** as a colorless oil in 95% isolated yield (51.0 mg, 0.144 mmol). The spectral data of **20b** are the same as the product obtained from the reductive ring opening of *cis*-**16b**. The ^{1}H NMR spectrum of the crude reaction mixture showed the ratio of **20b**/**24b** > 99:1

*4.9.9. Reductive Ring Opening of cis-**17a**.* The general procedure for the reductive ring opening described above was followed, starting with aziridine *cis*-**17a** (53.4 mg, 0.15 mmol, 1.0 equiv), SmI_2 (4.0 equiv), *N*,*N*-dimethylethanolamine (0.12 mL, 1.2 mmol, 8.0 equiv), and dry THF (2.0 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) held at 0 °C for 1 h. The ^{1}H NMR spectrum of the crude reaction mixture showed that **21a** and **25a** were present in a ratio of 23:1. Purification by silica-gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded (*S*)-**21a** as a white solid in 84% isolated yield (45.2 mg, 0.126 mmol) and **25a** as a colorless oil in 4% isolated yield (2.0 mg, 0.0056 mmol). Spectral data for **21a**: white solid; mp 60−61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.14 (s, 9H), 0.75 (td, 1H, J = 14, 4.5 Hz), 0.84 (td, 1H, J = 14, 4.0 Hz), 1.17 (t, 3H, J = 7 Hz), 2.52 (td, 1H, J = 14, 4.5 Hz), 2.63 (td, 1H, J = 14, 4.0 Hz), 2.79−2.90 (m, 2H), 4.08 (qd, 2H, J = 7.2, 1.5 Hz), 4.81−4.90 (m, 1H), 5.57 (d, 1H, J = 8 Hz), 7.24−7.30 (m, 1H), 7.30−7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −2.2, 10.2, 14.0, 41.9, 49.9, 54.5, 61.0, 126.6, 128.2, 128.9, 140.3, 170.5; IR (thin film) 3277 (br, s), 2955 (w), 1736 (s), 1144 (s) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{28}NO_4SiS^+$, 358.1508; found, 358.1509; $[\alpha]_D^{20}$ = −21.7 (c 0.87, CH_2Cl_2) on 98% ee (*S*)-**21a**. Spectral data for **25a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.11−1.16 (m, 2H), 1.24 (t, 3H, J = 7.2 Hz), 3.05−3.10 (m, 2H), 3.90 (s, 2H), 4.16 (q, 2H, J = 7.2 Hz), 4.53 (s, 2H), 7.27−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −2.0, 10.3, 14.2, 46.9, 50.0, 51.8, 61.3, 128.1, 128.5, 128.8, 135.5, 169.6; IR (thin film) 2955 (w), 1746 (s), 1333 (s), 1142 (s) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{28}NO_4SiS^+$, 358.1508; found, 358.1530.

*4.9.10. Reductive Ring Opening of cis-**18a**.* The general procedure for the reductive ring opening described above was followed, except that 2.5 equiv of SmI_2 and 5 equiv of DMEA were used. Starting from *cis*-**18a** (47 mg, 0.19 mmol), purification of the product by silica-gel chromatography (18 mm × 300 mm, 1:5 EtOAc/hexanes as eluent) gave **22a** as a colorless semisolid in 52% isolated yield (24 mg, 0.1 mmol), along with the α-amino ester resulting from the cleavage of the N−C3 bond as a colorless semisolid in 13% isolated yield (6 mg, 0.025 mmol). TLC and spectral data for **22a**: R_f = 0.15 (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12 (t, 3H, J = 7.1 Hz), 1.98 (s, 3H), 2.77 (dd, 1H, J = 15.4, 6.0 Hz), 2.87 (dd, 1H, J = 15.7, 6.0 Hz), 4.04 (q, 2H, J = 7.1 Hz), 5.36−5.43 (m, 1H), 6.60 (d, 1H, J = 8.0 Hz), 7.20−7.32 (m, 5H). The ^{1}H NMR spectral data match those previously reported for this compound.[13b]

*4.9.11. Reductive Ring Opening of cis-**27a**.* The general procedure for the reductive ring opening described above was followed, except that 5.0 equiv of SmI_2 and 10 equiv of DMEA were used. Starting from *cis*-**27a**[18] (19 mg, 0.10 mmol), purification of the product by silica-gel chromatography (18 mm × 300 mm, 1:1:4 Et_2O/CH_2Cl_2/hexanes as eluent) gave **31a** as a colorless oil in 75% isolated yield (14.4 mg, 0.0746 mmol). Spectral data for **31a**: ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 1.25 (t, 3H, J = 7.1 Hz), 3.39 (s, 2H), 3.78 (s, 2H), 4.17 (q, 2H, J = 7.2 Hz), 7.20−7.35 (m, 5H) (N−H proton not located). The ^{1}H NMR spectral data match those previously reported for this compound.[36]

*4.9.12. Reductive Ring Opening of cis-**29a**.* The general procedure for the reductive ring opening described above was followed, except that 5.0 equiv of SmI_2 and 10 equiv of DMEA were used. Starting from *cis*-**29a**[7a] (35 mg, 0.10 mmol), purification of the product by silica-gel chromatography (18 mm × 300 mm, 1:1:4 Et_2O/CH_2Cl_2/hexanes as eluent) gave **33a** as a colorless oil in 69% isolated yield (25 mg, 0.069 mmol). Spectral data for **33a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3H, J = 7.2 Hz), 3.25 (s, 2H), 3.82 (s, 2H), 4.04 (q, 2H, J = 7.2 Hz), 5.27 (s, 1H), 7.15−7.51 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 50.3, 54.9, 59.9, 70.3, 127.0, 127.1, 128.28, 128.33, 128.4, 128.7, 139.2, 142.1, 171.6.

*4.9.13. Reductive Ring Opening of cis-**29b**.* The general procedure for the reductive ring opening described above was followed, starting with *cis*-**29b**[7a] (44 mg, 0.12 mmol). Purification of the product by silica-gel chromatography (18 mm × 300 mm, 1:5 EtOAc/hexanes as eluent) gave a 1:1.4 mixture of β-amino ester **30b** (22% NMR yield) and unreacted *cis*-**29b** (31% NMR yield). The ^{1}H NMR spectrum of the crude reaction mixture indicated the formation of amine **34** in 39% yield. Extending the reaction time from 40 min to 2 h for the ring-opening reaction of *cis*-**29b** (42 mg, 0.12 mmol) at room temperature gave **30b** (8.6 mg, 0.024 mmol) in 22% isolated yield and amine **34** in 52% isolated yield. The unreacted *cis*-**29b** was isolated with a 20% recovery. Spectral data for **30b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90−1.04 (m, 2H), 1.05−1.23 (m, 2H), 1.20 (t, 3H, J = 7.1 Hz), 1.45−1.54 (m, 1H), 1.60−1.80 (m, 6H), 2.34 (dd, 1H, J = 14.5, 7.0 Hz), 2.47 (dd, 1H, J = 14.5, 5.3 Hz), 2.77 (dt, 1H, J = 7.0, 5.3 Hz), 4.03−4.14 (m, 2H), 4.94 (s, 1H), 7.15−7.19 (m, 2H), 7.23−7.28 (m, 4H), 7.35−7.41 (m, 4H) (N−H proton not located); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 26.5, 26.6, 26.7, 28.4, 29.5, 36.0, 40.9, 56.8, 60.2, 64.1, 126.89, 126.91, 127.4, 127.6, 128.33, 128.34, 144.2, 144.4, 172.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{32}NO_2$, 366.2433; found, 366.2431. Spectral data for **34**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.84 (bs, 2H), 5.20 (s, 1H), 7.18−7.23 (m, 2H), 7.26−7.32 (m, 4H), 7.33−7.37 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 59.7, 126.88, 126.92, 128.4, 145.6. The ^{1}H and ^{13}C NMR

spectral data for **34** match those provided by the source for this compound.

*4.9.14. Reductive Ring Opening of **35**.* The general procedure for the reductive ring opening described above was followed, starting with trisubstituted aziridine **35**[20] (76 mg, 0.25 mmol, 99% ee) and 5.0 equiv of SmI_2. The ^1H NMR spectrum of the crude reaction mixture indicated that a mixture of *anti*-**36**, *syn*-**36**, and **37** was present in a ratio of 1.28:0.28:1, respectively. Purification of the products by silica-gel chromatography (18 mm × 200 mm, 1:10 to 1:6 EtOAc/hexanes as eluent) gave *anti*-**36** as a white solid (mp 53−55 °C) in 43% isolated yield (32.7 mg, 0.106 mmol), *syn*-**36** as a white solid (mp 89−91 °C) in 9% isolated yield (6.6 mg, 0.021 mmol), and **37** as a colorless oil in 30% isolated yield (23.2 mg, 0.0755 mmol). Spectral data for *anti*-**36**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7.1 Hz), 1.20 (d, 3H, J = 7.0 Hz), 1.39 (s, 9H), 2.87 (brt, 1H, J = 6.5 Hz), 4.01 (q, 2H, J = 7.1 Hz), 4.81 (brs, 1H), 5.81 (brs, 1H), 7.16−7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 15.4, 28.3, 45.3, 56.7, 60.6, 79.4, 126.3, 127.3, 128.4, 141.0, 155.4, 174.9; IR (thin film) 3355 (br, w), 2978 (m), 1721 (s), 1171 (s) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}NO_4^+$, 308.1862; found, 308.1860; $[\alpha]_D^{20} = -40.1$ (c 0.5, CH_2Cl_2) on 99% ee material. Spectral data for *syn*-**36**: ^1H NMR (600 MHz, $CDCl_3$) δ 1.11 (t, 3H, J = 7.2 Hz), 1.13 (d, 3H, J = 7.2 Hz), 1.39 (s, 9H), 2.87 (brs, 1H), 3.96−4.08 (m, 2H), 4.97 (brs, 1H), 5.27 (brs, 1H), 7.19−7.25 (m, 3H), 7.26−7.31 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.1, 14.0, 28.3, 45.4, 56.5, 60.6, 79.6, 126.8, 127.4, 128.4, 140.2, 155.1, 173.7; IR (thin film) 3380 (s), 2980 (m), 1728 (s), 1686 (s), 1520 (s), 1173 (s) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}NO_4^+$, 308.1862; found, 308.1855; $[\alpha]_D^{20} = -26.0$ (c 0.5, CH_2Cl_2) on 99% ee material. Spectral data for **37** (compound **37** appeared to be a colorless-oil mixture of two rotamers at room temperature in a ratio of 1.2:1): ^1H NMR (600 MHz, $CDCl_3$) δ 1.21 (t, 3H, J = 7.2 Hz), 1.27−1.50 (m, 12H), 3.82−4.64 (m, 5H), 7.16−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 15.4, 15.8, 28.3, 49.7, 50.8, 54.8, 55.4, 60.9, 80.4, 80.6, 127.0, 127.2, 127.3, 128.0, 128.3, 128.6, 138.2, 139.2, 155.4, 155.5, 172.1, 172.3. The ^1H NMR data match those previously reported for this compound.[37]

*4.9.15. Determination of the Relative Stereochemistry of anti-**36**.* Trifluoroacetic acid (0.240 mL, 357 mg, 3.13 mmol, 35.6 equiv) was added to a solution of *anti*-**36** (27 mg, 0.088 mmol, 1.0 equiv) in CH_2Cl_2 (0.24 mL). After the reaction mixture was stirred at room temperature under nitrogen overnight, it was concentrated and diluted with 0.3 mL of H_2O. The pH of the mixture was adjusted to ∼10 with sat aq $NaHCO_3$ (ca. 10 mL), and then the mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification of the product by silica-gel chromatography (18 mm × 150 mm, 1:1 EtOAc/hexanes as eluent) gave ethyl 3-amino-2-methyl-3-phenylpropanoate **60** as a colorless oil in 74% isolated yield (13.5 mg, 0.065 mmol). Spectral data for ethyl 3-amino-2-methyl-3-phenylpropanoate: ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 7.2 Hz), 1.26 (t, 3H, J = 7.2 Hz), 1.64 (brs, 2H), 2.60−2.72 (m, 1H), 4.00 (d, 1H, J = 9.4 Hz), 4.17 (q, 2H, J = 7.2 Hz), 7.21−7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 15.4, 48.1, 59.1, 60.4, 127.0, 127.5, 128.5, 143.6, 175.9. The ^1H NMR data match those previously reported for the anti isomer but not those of the syn isomer.[38]

4.10. Procedures for the Syntheses of Protected Forms of L-DOPA and (*R*)-β³-DOPA. *4.10.1. 4-((2S,3S)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl)aziridin-2-yl)-1,2-phenylene Diacetate (**54**).* To a flame-dried 25 mL Schlenk flask equipped with a stir bar and filled with nitrogen were added (*R*)-VAPOL (54 mg, 0.10 mmol), $B(OPh)_3$ (87 mg, 0.30 mmol), amine **52**[7d] (599 mg, 2.00 mmol); dry toluene (4 mL) was added to dissolve the reagents. The flask was then sealed, and the reaction mixture was stirred at room temperature for 1 h. Thereafter, 4 Å of powdered molecular sieves (600 mg, freshly flame-dried) were added to the reaction flask, followed by the addition of aldehyde **50**[39] (467 mg, 2.10 mmoL, 1.05 equiv). to this solution was rapidly added ethyl diazoacetate (EDA) **53** (0.30 mL, 2.4 mmoL, 1.2 equiv). After the resulting mixture was stirred for 20 h at room temperature, it was diluted by the addition of hexane (12 mL). The reaction mixture was then filtered through a Celite pad into a 100 mL round-bottomed flask. The reaction flask was rinsed with EtOAc (6 mL × 3), and the rinse was filtered through the same Celite pad. The combined filtrate was concentrated in vacuo, followed by exposure to high vacuum (0.05 mmHg) to afford the crude aziridine as a yellow oil. Purification of the crude aziridine by silica-gel chromatography (40 mm × 210 mm column, 2:1 hexanes/EtOAc as eluent) afforded pure *cis*-aziridine **54** as a white solid (mp 65−67 °C on >98.5% ee material) in 98% isolated yield (1.15 g, 1.95 mmol). The optical purity of **54** was determined to be >98.5% ee by HPLC analysis (CHIRALCEL OD-H column, 85:15 hexane/2-propanol at 222 nm, flow rate: 1 mL/min). Retention times: R_t = 7.18 min (minor enantiomer, *ent*-**54**) and R_t = 8.46 min (major enantiomer, **54**). Spectral data for **54**: R_f = 0.19 (1:2 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, 3H, J = 7.1 Hz), 2.21 (s, 6H), 2.25 (s, 3H), 2.26 (s, 6H), 2.27 (s, 3H), 2.59 (d, 1H, J = 6.8 Hz), 3.09 (d, 1H, J = 6.8 Hz), 3.65 (s, 3H), 3.68 (s, 1H), 3.69 (s, 3H), 3.91−4.03 (m, 2H), 7.04−7.10 (m, 3H), 7.17 (s, 2H), 7.24−7.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 16.15, 16.22, 20.59, 20.60, 46.4, 47.2, 59.5, 59.6, 60.8, 76.8, 122.6, 122.9, 126.0, 127.3, 127.7, 130.6, 130.8, 134.2, 137.5, 137.6, 141.2, 141.4, 155.9, 156.2, 167.7, 168.0, 168.2; IR (thin film) 2932 (m), 1773 (vs), 1746 (s), 1213 (vs) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{34}H_{40}NO_8^+$, 590.2754; found, 590.2769; $[\alpha]_D^{20} = -28.2°$ (c 1.0, CH_2Cl_2) on >98.5% ee (by HPLC) material.

*4.10.2. 4-((2S,3S)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl)aziridin-2-yl)-1,2-phenylene bis(2,2-dimethylpropanoate) (**55**).* The procedure for the synthesis of aziridine **54** was followed, starting with aldehyde **51**[40] (643 mg, 2.10 mmoL, 1.05 equiv). Purification of the crude product by silica-gel chromatography (40 mm × 210 mm column, 5:1 hexanes/EtOAc as eluent) afforded pure *cis*-aziridine **55** as a white solid (mp 64−66 °C on 98% ee material) in 97% isolated yield (1.31 g, 1.94 mmol). The optical purity of **55** was determined to be 98% ee by HPLC analysis (Chiralpak AD column, 95:5 hexane/2-propanol at 222 nm, flow- rate: 0.7 mL/min). Retention times: R_t = 8.68 min (minor enantiomer, *ent*-**55**) and R_t = 10.23 min (major enantiomer, **55**). Spectral data for **55**: R_f = 0.21 (1:5 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 7.0 Hz), 1.30 (s, 9H), 1.32 (s, 9H), 2.20 (s, 6H), 2.24 (s, 6H), 2.56 (d, 1H, J = 6.8 Hz), 3.08 (d, 1H, J = 6.8 Hz), 3.64 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H), 3.90−4.03 (m, 2H), 6.98 (d, 1H, J = 8.0 Hz), 7.07 (s, 2H), 7.11 (d, 1H, J = 1.5 Hz), 7.16 (s, 2H), 7.25 (dd, 1H, J = 8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 16.18, 16.22, 27.18, 27.23, 39.0, 39.1, 46.2, 47.3, 59.5, 59.6, 60.7, 76.9, 122.6, 122.8, 125.6, 127.3, 127.7, 130.6, 130.7, 133.7, 137.55, 137.61, 141.7, 141.9, 155.9, 156.1, 167.8, 175.6, 175.8; IR (thin film) 2977 (s), 1761 (vs), 1482 (s), 1119 (vs) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{40}H_{52}NO_8^+$, 674.3693; found, 674.3694; $[\alpha]_D^{20} = -34.2°$ (c 1.0, CH_2Cl_2) on 98% ee (by HPLC) material.

*4.10.3. (S)-4-(2-((tert-Butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)-1,2-phenylene Bis(2,2-dimethylpropanoate) (**56**).* To a oven-dried 25 mL round-bottomed flask equipped with a stir bar and filled with nitrogen were added aziridine **55** (67.4 mg, 0.100 mmol, 98% ee), $Pd(OH)_2$ (28.0 mg, 0.020 mmol, $Pd(OH)_2$ on carbon 20%, moisture ≤50%), di*tert*-butyl dicarbonate (33 mg, 0.15 mmol), and methanol (10 mL). The flask was sealed with a rubber septum, and a needle connected to a vacuum line was used to apply vacuum in the flask through the septum. The vacuum was applied for a few seconds with vigorous stirring of the reaction mixture. Then the vacuum was stopped, and a hydrogen balloon was connected to the flask by a needle through the septum. This process was repeated four times. The suspension was stirred at room temperature under hydrogen for 17 h and then filtered through a pad of Celite. The filter cake was washed with EtOAc (5 mL) and DCM (3 mL × 3). The combined filtrate was concentrated to give a light-yellow oil. Purification of the crude product by column chromatography on silica gel (20 mm × 160 mm, hexanes/EtOAc 5:1) gave α-amino ester **56** as a colorless oil (42.2 mg, 0.0855 mmol, 86%). Spectral data for **56**: R_f = 0.20 (1:5 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, 3H, J = 7.0 Hz), 1.30 (s, 18H), 1.41 (s, 9H), 3.06 (d, 2H, J = 6.0 Hz), 4.07−4.18 (m, 2H), 4.50 (dt, 1H, J = 7.5, 6.0 Hz), 5.01 (d, 1H, J = 7.5 Hz), 6.87 (s, 1H), 6.97 (d, 1H, J = 8.2 Hz), 7.02 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 27.2, 28.3, 37.5, 39.06, 39.09, 54.3, 61.5, 79.9, 123.2, 124.2, 127.0, 134.5, 141.5, 142.3, 155.0, 171.5, 175.6, 175.8 (one sp^3 carbon not located); IR (thin

film) 2977 (s), 1761 (vs), 1482 (s), 1119 (vs) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{40}NO_8^+$, 494.2754; found, 494.2751; $[\alpha]_D^{20}$ = +27.8° (*c* 1.0, CH_2Cl_2) on 98% ee material. (The optical purity was assumed to be unchanged from that of **55**.)

*4.10.4. 4-((2S,3S)-3-(Ethoxycarbonyl)-1-tosylaziridin-2-yl)-1,2-phenylene Diacetate (**57**).* To a flame-dried 100 mL round-bottomed flask equipped with a stir bar and filled with nitrogen were added room-temperature aziridine **54** (467 mg, 0.792 mmol) and anisole (4.1 mL). The resulting solution was cooled to 0 °C in an ice bath, and trifluoroacetic acid (4.1 mL) was rapidly added. The ice bath was then removed, and the reaction mixture was stirred for 40 min at room temperature. The reaction mixture was quenched by careful addition of sat aq Na_2CO_3 (30 mL) and H_2O (10 mL), followed by the addition of Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo, followed by exposure to high vacuum (0.05 mmHg) for 4 h to give a yellow oil, to which was added 6.5 mL of $CH_2CI_2/CHCl_3$ (1:1) and Et_3N (0.33 mL, 2.4 mmol). The resulting solution was cooled to 0 °C, and a portion of tosyl chloride (228 mg, 1.20 mmol) was added. The mixture was then stirred at 0 °C for 15 h. Thereafter, additional portions of both tosyl chloride (228 mg, 1.20 mmol) and Et_3N (0.33 mL, 2.4 mmol) were added to the reaction mixture at room temperature. After the mixture was stirred for 26 h at room temperature, the reaction was quenched with 12 mL of sat aq NH_4Cl and 2.5 mL of H_2O. The aqueous layer was extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated to give a dark-brown oil. Purification by silica-gel chromatography (25 mm × 160 mm, 2:1 hexanes/EtOAc as eluent) afforded *cis*-**57** as a light-yellow oil in 70% yield (258 mg, 0.559 mmol). Spectral data for **57**: R_f = 0.14 (1:2 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.1 Hz), 2.236 (s, 3H), 2.240 (s, 3H), 2.43 (s, 3H), 3.66 (d, 1H, *J* = 7.5 Hz), 3.89−4.02 (m, 2H), 4.03 (d, 1H, *J* = 7.5 Hz), 7.07 (d, 1H, *J* = 8.3 Hz), 7.13 (d, 1H, *J* = 2.0 Hz), 7.17 (dd, 2H, *J* = 8.3, 2.0 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.88 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 20.55, 20.60, 21.7, 43.4, 44.3, 61.9, 122.7, 123.3, 125.8, 128.1, 129.9, 130.0, 133.7, 141.8, 142.3, 145.4, 164.1, 167.8, 168.0; IR (thin film) 2986 (w), 1773 (vs), 1734 (m), 1210 (vs), 1165 (s) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{24}NO_8S^+$, 462.1223; found, 462.1234; $[\alpha]_D^{20}$ = +15.6° (*c* 1.0, CH_2Cl_2) on >98.5% ee material. (The optical purity was assumed to be unchanged from that of **54**.)

*4.10.5. 4-((2S,3S)-3-(Ethoxycarbonyl)-1-((2-(trimethylsilyl)ethyl)-sulfonyl)aziridin-2-yl)-1,2-phenylene Diacetate (**58**).* to a flame-dried 100 mL round-bottomed flask equipped with a stir bar and filled with nitrogen were added room-temperature aziridine **54** (366 mg, 0.621 mmol) and anisole (3.1 mL). The resulting solution was cooled to 0 °C in an ice bath, and trifluoroacetic acid (3.1 mL) was rapidly added. The ice bath was then removed, and the reaction mixture was stirred for 40 min at room temperature. The reaction mixture was quenched by careful addition of saturated aq Na_2CO_3 (25 mL) and H_2O (10 mL), followed by addition of Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 4 h to give a yellow oil, which was then dissolved in a mixture of CH_2Cl_2 (2 mL) and Et_3N (0.9 mL). After the solution was cooled to 0 °C in an ice bath, 2-(trimethylsilyl)ethanesulfonyl chloride (0.12 mL, 0.93 mmol) was added dropwise to the reaction mixture at 0 °C. The ice bath was then removed, and the reaction mixture was stirred at room temperature for 17 h. Thereafter, additional portions of both 2-(trimethylsilyl)ethanesulfonyl chloride (0.12 mL, 0.93 mmol) and Et_3N (0.9 mL) were added to the reaction mixture at room temperature. After the mixture was stirred for 23 h at room temperature, the reaction was quenched with 2.5 mL of sat aq NH_4Cl and 1 mL of H_2O. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated to give a dark-brown oil. Purification by silica-gel chromatography (25 mm × 160 mm, 3:1 hexanes/EtOAc as eluent) afforded *cis*-**58** as a light-yellow oil in 78% yield (0.228 g, 0.483 mmol). Spectral data for **58**: R_f = 0.20 (1:3 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.03 (t, 3H, *J* = 7.0 Hz), 1.12−1.20 (m, 2H), 2.26 (s, 6H), 3.16−3.24 (m, 2H), 3.66 (d, 1H, *J* = 7.5 Hz), 3.97−4.09 (m, 2H), 4.02 (d, 1H, *J* = 7.5 Hz), 7.15 (d, 1H, *J* = 8.2 Hz), 7.25 (d, 1H, *J* = 1.9 Hz), 7.30 (dd, 1H, *J* = 8.2 Hz, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.1, 9.5, 13.8, 20.57, 20.62, 43.5, 43.6, 49.5, 62.0, 122.8, 123.4, 125.8, 130.1, 142.0, 142.4, 164.2, 167.9, 168.0; IR (thin film) 2955 (m), 1777 (s), 1208 (s), 1177 (s) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{30}NO_8SiS^+$, 472.1461; found, 472.1449; $[\alpha]_D^{20}$ = +27.5° (*c* 1.0, CH_2Cl_2) on >98.5% ee material. (The optical purity was assumed to be unchanged from that of **54**.)

*4.10.6. 4-((2S,3S)-3-(Ethoxycarbonyl)-1-((2-(trimethylsilyl)ethyl)-sulfonyl)aziridin-2-yl)-1,2-phenylene Bis(2,2-dimethylpropanoate) (**59**).* To a flame-dried 100 mL round-bottomed flask equipped with a stir bar and filled with nitrogen were added room-temperature aziridine **55** (674 mg, 1.00 mmol) and anisole (8.9 mL). The resulting solution was cooled to 0 °C in a ice bath, and trifluoroacetic acid (8.9 mL) was rapidly added. The ice bath was removed, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was quenched by the careful addition of saturated aq Na_2CO_3 (68 mL) and H_2O (35 mL), followed by the addition of Et_2O (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo, followed by exposure to high vacuum (0.05 mmHg) for 4 h to give a yellow oil, which was then dissolved in a mixture of CH_2Cl_2 (3.5 mL) and Et_3N (1.5 mL). After the solution was cooled to 0 °C, 2-(trimethylsilyl)ethanesulfonyl chloride (0.20 mL, 1.5 mmol) was added dropwise to the reaction mixture at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 14 h. Thereafter, additional portions of both 2-(trimethylsilyl)-ethanesulfonyl chloride (0.20 mL, 1.5 mmol) and Et_3N (1.5 mL) were added to the reaction mixture at room temperature. After the mixture was stirred for 22 h at room temperature, the reaction was quenched with 4 mL of sat aq NH_4Cl and 1.5 mL of H_2O. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (6 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated to give a dark-brown oil. Purification by silica-gel chromatography (25 mm × 160 mm, 5:1 hexanes/EtOAc as eluent) afforded *cis*-**59** as a light-yellow oil in 86% yield (0.475 g, 0.855 mmol). Spectral data for **59**: R_f = 0.20 (1:5 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.06 (t, 3H, *J* = 7.1 Hz), 1.11−1.21 (m, 2H), 1.31 (s, 9H), 1.32 (s, 9H), 3.17−3.26 (m, 2H), 3.66 (d, 1H, *J* = 7.5 Hz), 3.98−4.07 (m, 2H), 4.02 (d, 1H, *J* = 7.5 Hz), 7.09 (d, 1H, *J* = 8.3 Hz), 7.18 (d, 1H, *J* = 1.8 Hz), 7.27 (dd, 1H, *J* = 8.3 Hz, *J* = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.1, 9.5, 13.8, 27.10, 27.14, 39.0, 39.1, 43.2, 43.7, 49.4, 61.9, 122.7, 123.3, 125.4, 129.5, 142.4, 142.9, 164.2, 175.4, 175.6; IR (thin film) 2977 (m), 1761 (vs), 1117 (s) cm^{-1}; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{26}H_{45}N_2O_8SiS^+$, 573.2666; found, 573.2675; $[\alpha]_D^{20}$ = +26.9° (*c* 1.0, CH_2Cl_2) on 98% ee material. (The optical purity was assumed to be unchanged from that of **55**).

*4.10.7. Reductive Ring Opening of **57**.* The general procedure for the reductive ring opening described above was followed, starting with aziridine **57** (228 mg, 0.494 mmol), 2.5 equiv of SmI_2, and 5 equiv of DMEA. The ^{1}H NMR spectrum of the crude reaction mixture indicated a complex mixture of several products due to partial cleavage of the acetate group on the benzene ring. To this mixture were added Ac_2O (0.2 mL) and Et_3N (0.16 mL). After the reaction was stirred at room temperature for 30 min, it was quenched by the addition of EtOH (0.1 mL) and H_2O (2.5 mL). The resulting mixture was extracted with EtOAc (3 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated to give a yellow oil. Purification by silica-gel chromatography (20 mm × 160 mm, 1:1.5 EtOAc/hexanes as eluent) gave **61A** as a colorless oil in 76% isolated yield (173 mg, 0.373 mmol) and **61B** as a light-yellow oil in 8% isolated yield (17.5 mg, 0.0377 mmol). Spectral data for **61A**: R_f = 0.23 (1:1.5 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, 3H, *J* = 7.1 Hz), 2.22 (s, 6H), 2.33 (s, 3H), 2.68 (dd, 1H, *J* = 16.2, 6.2 Hz), 2.75 (dd, 1H, *J* = 16.2, 6.4 Hz), 3.99 (q, 2H, *J* = 7.1 Hz), 4.70 (dt, 1H, *J* = 7.5, 6.2 Hz), 5.97 (d, 1H, *J* = 7.8 Hz), 6.90−6.98 (m, 3H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.54 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.5, 20.6, 21.4, 41.0, 53.6, 61.0, 121.8, 123.3, 124.5, 126.9, 129.5, 137.1, 138.0, 141.4, 141.8, 143.4,

167.8, 167.9, 170.4; IR (thin film) 3279 (m), 2984 (w), 2930 (w), 1773 (s), 1734 (s), 1211 (s), 1161 (s) cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{26}NO_8S^+$, 464.1379; found, 464.1381; $[\alpha]_D^{20}$ = +45.2° (*c* 1.0, CH_2Cl_2) on >98% ee material. (The optical purity was assumed to be unchanged from that of **54**.) Spectral data for **61B**: R_f = 0.38 (1:1.5 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, 3H, *J* = 7.1 Hz), 2.26 (s, 6H), 2.42 (s, 3H), 3.93 (s, 2H), 3.99 (q, 2H, *J* = 7.1 Hz), 4.46 (s, 2H), 7.09 (s, 1H), 7.12 (s, 2H), 7.30 (d, 2H, *J* = 8.2 Hz), 7.73 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 20.6, 20.7, 21.6, 46.8, 50.5, 61.2, 123.5, 123.6, 126.5, 127.4, 129.6, 134.0, 136.7, 141.9, 142.2, 143.6, 168.1, 168.2, 168.6; IR (thin film) 2984 (w), 2934 (w), 1773 (vs), 1213 (s) cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{26}NO_8S^+$, 464.1379; found, 464.1381.

4.10.8. Reductive Ring Opening of ***58****.* The general procedure for the reductive ring opening described above was followed, starting with aziridine **58** (236 mg, 0.500 mmol), 4 equiv of SmI_2, and 8 equiv of DMEA. The ^1H NMR spectrum of the crude reaction mixture indicated a complex mixture of several products due to partial cleavage of the acetate group on the benzene ring. To this mixture were added Ac_2O (0.63 mL) and Et_3N (0.5 mL). After the reaction was stirred at room temperature for 40 min, it was quenched by the addition of EtOH (0.32 mL) and H_2O (9 mL). The resulting mixture was extracted with EtOAc (10 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated to give a yellow oil. Purification by silica-gel chromatography (20 mm × 160 mm, 1:2 EtOAc/hexanes as eluent) gave **62A** as a colorless oil in 69% isolated yield (164 mg, 0.346 mmol) and **62B** as a light-yellow oil in 19% isolated yield (45 mg, 0.095 mmol). Spectral data for **62A**: R_f = 0.21 (1:2 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ −0.09 (s, 9H), 0.78−0.93 (m, 2H), 1.19 (t, 3H, *J* = 7.1 Hz), 2.26 (s, 6H), 2.59−2.78 (m, 2H), 2.80−2.89 (m, 2H), 4.06−4.13 (m, 2H), 4.87 (dt, 1H, *J* = 8.1, 6.4 Hz), 5.70 (d, 1H, *J* = 8.1 Hz), 7.16 (d, 1H, *J* = 8.7 Hz), 7.19−7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.2, 10.2, 14.0, 20.575, 20.584, 41.6, 50.1, 53.6, 61.2, 121.9, 123.7, 124.6, 139.1, 141.7, 142.2, 167.8, 168.0, 170.5; IR (thin film) 3283 (m), 2955 (m), 1773 (vs), 1734 (vs), 1211 (s), 1143 (s) cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ calcd for $C_{20}H_{35}N_2O_8SiS^+$, 491.1883; found, 491.1894; $[\alpha]_D^{20}$ = +27.0° (*c* 1.0, CH_2Cl_2) on >98.5% ee material (the optical purity was assumed to be unchanged from **54**). Spectral data for **62B**: R_f = 0.27 (1:2 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.08−1.16 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz), 2.26 (s, 6H), 3.04−3.11 (m, 2H), 3.93 (s, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 4.52 (s, 2H), 7.12−7.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.0, 10.2, 14.1, 20.59, 20.63, 46.8, 50.0, 50.9, 61.4, 123.2, 123.7, 126.3, 134.4, 141.9, 142.3, 168.1, 168.2, 169.5; IR (thin film) 2955 (w), 2930 (w), 1773 (s), 1742 (s), 1211 (s) cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+NH_4]^+$ calcd for $C_{20}H_{35}N_2O_8SiS^+$, 491.1883; found, 491.1897.

4.10.9. Reductive Ring Opening of ***59****.* The general procedure for the reductive ring opening described above was followed, starting with aziridine **59** (111 mg, 0.200 mmol, 98% ee) and 4.0 equiv of SmI_2. The ^1H NMR spectrum of the crude reaction mixture indicated a mixture of C−N cleavage product **63A** and C−C cleavage product **63B** was obtained with a ratio of 4.3:1. Purification by silica-gel chromatography (20 mm × 160 mm, 1:3 EtOAc/hexanes as eluent) gave **63A** as a yellow oil in 74% isolated yield (81.8 mg, 0.147 mmol) and **63B** as a light-yellow oil in 16% isolated yield (18.2 mg, 0.0326 mmol). Spectral data for **63A**: R_f = 0.25 (1:3 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ −0.11 (s, 9H), 0.75−0.90 (m, 2H), 1.18 (t, 3H, *J* = 7.2 Hz), 1.29 (s, 9H), 1.30 (s, 9H), 2.55−2.75 (m, 2H), 2.82 (d, 2H, *J* = 6.5 Hz), 4.07 (q, 2H, *J* = 7.1 Hz), 4.84 (dt, 1H, *J* = 8.0, 6.5 Hz), 5.70 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 8.4 Hz), 7.13 (d, 1H, *J* = 2.0 Hz), 7.19 (dd, 1H, *J* = 8.4, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.2, 10.2, 14.0, 27.11, 27.13, 39.05, 39.06, 41.6, 50.0, 53.7, 61.1, 121.8, 123.7, 124.3, 138.6, 142.2, 142.6, 170.4, 175.4, 175.5; IR (thin film) 3283 (m), 2977 (s), 1763 (vs), 1736 (s), 1117 (s) cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+NH_4]^+$ calcd for $C_{26}H_{47}N_2O_8SiS^+$, 575.2822; found, 575.2842; $[\alpha]_D^{20}$ = +26.0° (*c* 1.0, CH_2Cl_2) on 98% ee material. (The optical purity was assumed to be unchanged from that of **55**.) Spectral data for **63B**: R_f = 0.39 (1:3 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.09−1.16 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.31 (s, 18H), 3.04−3.13 (m, 2H), 3.92 (s, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 4.52 (s, 2H), 7.06−7.11 (m, 2H), 7.17 (dd, 1H, *J* = 8.4, 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.0, 10.2, 14.1, 27.18, 27.21, 39.10, 39.13, 46.7, 50.0, 50.9, 61.4, 123.4, 123.7, 126.1, 133.9, 142.4, 142.8, 169.5, 175.7, 175.8; IR (thin film) 2977 (s), 1761 (vs), 1507 (m), 1337 (m), 1256 (m), 1117 (vs) cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+NH_4]^+$ calcd for $C_{26}H_{47}N_2O_8SiS^+$, 575.2822; found, 575.2834.

*4.10.10. (R)-4-(1-((tert-Butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)-1,2-phenylene Bis(2,2-dimethylpropanoate) (****64****).* To a oven-dried 10 mL Schlenk flask equipped with a stir bar and filled with nitrogen were added **63A** (38 mg, 0.068 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.9 mg, 0.007 mmol, 0.1 equiv), Et_3N (19 μL, 14 mg, 0.14 mmol, 2.0 equiv), and CH_2Cl_2 (0.32 mL). The flask was sealed, and the reaction mixture was stirred for 2 h at room temperature and then stirred at 40 °C for 15 h. After the reaction mixture was cooled to room temperature, 0.5 mL of 1 N HCl was added to the flask, followed by the addition of EtOAc (5 mL). The organic layer was separated, washed with brine (0.3 mL × 2), dried with Na_2SO_4, and concentrated to give a yellow oil, which was then dissolved in THF (0.65 mL) in a 10 mL Schlenk flask filled with nitrogen. To this solution was dropwise added TBAF (0.31 mL, 1 M in THF, 0.31 mmol) at room temperature. After the reaction mixture was stirred at room temperature under nitrogen for 1.5 h, it was concentrated by rotary evaporation and then high vacuum (0.5 mmHg) to give a bright-yellow oil. This oil was dissolved in a mixture of THF (0.2 mL) and Et_3N (0.2 mL). Then trimethylacetyl chloride (0.05 mL, 0.4 mmol) was added to the solution at room temperature. After the resulting reaction mixture was stirred for 15 min at room temperature under nitrogen, it was quenched by the addition of EtOH (0.1 mL) and H_2O (1.5 mL). The resulting mixture was extracted with EtOAc (2 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated to afford a yellow oil. Purification by silica-gel chromatography (20 mm × 120 mm, 1:3 EtOAc/hexanes as eluent) gave **64** as a light-yellow oil in 88% isolated yield (29.5 mg, 0.0598 mmol). Spectral data for **64**: R_f = 0.27 (1:3 EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, 3H, *J* = 7.2 Hz), 1.30 (s, 9H), 1.31 (s, 9H), 1.39 (brs, 9H), 2.62−2.92 (m, 2H), 4.06 (q, 2H, *J* = 7.2 Hz), 5.06 (brs, 1H), 5.47 (d, 1H, *J* = 7.5 Hz), 7.03 (d, 1H, *J* = 1.6 Hz), 7.06 (d, 1H, *J* = 8.4 Hz), 7.14 (dd, 1H, *J* = 8.4 Hz, *J* = 1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 27.20, 27.22, 28.3, 39.10, 39.12, 40.7, 50.6, 60.9, 79.8, 121.4, 123.5, 124.0, 139.7, 141.8, 142.5, 154.9, 170.7, 175.6, 175.8; IR (thin film) 3387 (m), 2978 (s), 2936 (m), 2874 (w), 1761 (vs), 1739 (s), 1723 (s), 1713 (s), 1256 (s), 1119 (vs) cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{26}H_{40}NO_8^+$, 494.2754; found, 494.2758; $[\alpha]_D^{20}$ = +23.6° (*c* 1.0, CH_2Cl_2) on 98% ee material. (The optical purity was assumed to be unchanged from that of **55**.)

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (b) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshnok, V., Eds.; Wiley: Hoboken, NJ, 2005.

(2) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Groselj, U.; Zass, E. *Synthesis* **2009**, 1−32.

(3) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656−1691.
(4) (a) For reviews on asymmetric aziridination, see Pellissier, H. *Tetrahedron* **2010**, *66*, 1509−1555. (b) Pellissier, H. *Adv. Synth. Catal.* **2014**, *356*, 1899−1935. (c) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881−7929.
(5) Gupta, A. K.; Mukherjee, M.; Hu, G.; Wulff, W. D. *J. Org. Chem.* **2012**, *77*, 7932.
(6) Hu, G.; Gupta, A. K.; Huang, R. H.; Mukherjee, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 14669−14675.
(7) (a) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518−4521. (b) Zhang, Y.; Desai, A.; Lu, Z.; Hu, G.; Ding, Z.; Wulff, W. D. *Chem.—Eur. J.* **2008**, *14*, 3785−3803. (c) Zhang, Y.; Lu, Z.; Wulff, W. D. *Synlett* **2009**, 2715−2739. (d) Mukherjee, M.; Gupta, A. K.; Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Org. Chem.* **2010**, *75*, 5643.
(8) Guan, Y.; Ding, Z.; Wulff, W. D. *Chem.—Eur. J.* **2013**, *19*, 15565−15571.
(9) (a) Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380−14381. (b) Desai, A.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 13100−13103. (c) Vetticatt, M.; Desai, A.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 13104−14107.
(10) (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347−1365. (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743.
(11) For a review on the preparation and chemistry of aziridine-2-carboxylates, see Ishikawa, T. *Heterocycles* **2012**, *85*, 2837−2877.
(12) For selected examples, see (a) Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* **1999**, *40*, 9325−9327. (b) Patwardhan, A. P.; Pulgam, V. R.; Zhang, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6199−6110. (c) Maguire, N. E.; McLaren, A. B.; Sweeney, J. B. *Synlett* **2003**, 1898−1900.
(13) (a) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660−6661. (b) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887−8912. (c) Ogawa, Y.; Kuroda, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1309−1333. (d) Kumamoto, T.; Nagayama, S.-I.; Hayashi, Y.; Kojima, H.; David, L.; Nakanishi, W.; Ishikawa, T. *Heterocycles* **2008**, *76*, 1155−1170. (e) The reductive ring opening of *trans*-**15a** has been reported to give only **19a** (82%).[13b]
(14) Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006−10010.
(15) Concellon, J. M.; Rodriguez-Solla, H.; del Amo, V.; Diaz, P. *J. Org. Chem.* **2010**, *75*, 2407−2410.
(16) Kim, S.; Jung, M. S.; Cho, C. H.; Schiesser, C. H. *Tetrahedron Lett.* **2001**, *42*, 943−945.
(17) Davis, A. L.; Korous, A. A.; Hartel, A. M. *Tetrahedron Lett.* **2013**, *54*, 3673−3674.
(18) Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185−7194.
(19) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099−2102.
(20) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892−8895.
(21) Jankovic, J. *J. Neurol., Neurosurg. Psychiatry* **2008**, *79*, 368−376.
(22) Waite, J. H.; Anderson, N. H.; Jewhurst, S.; Sun, C. *J. Adhes.* **2005**, *81*, 297−317.
(23) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106−112.
(24) Von Nussbaum, F.; Spiteller, P.; Ruth, M.; Steglich, W.; Wanner, G.; Gamblin, B.; Stievano, L.; Wagner, F. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 3292−3295.
(25) For a recent report on the synthesis of (*R*)-β^3-DOPA, see Nishimura, T.; Wang, J.; Nagaosa, M.; Okamoto, K.; Shintani, R.; Kwong, F.-Y.; Yu, W.-Y.; Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464−465.
(26) Ribière, P.; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2006**, *106*, 2249−2269.
(27) Ding, Z.; Osminski, W. E. G.; Ren, H.; Wulff, W. D. *Org. Process Res. Dev.* **2011**, *15*, 1089−1107.
(28) Hili, R.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4188−4191.
(29) Kulshrestha, A.; Schomaker, J. M.; Holmes, D.; Staples, R. J.; Jackson, J. E.; Borhan, B. *Chem.—Eur. J.* **2011**, *17*, 12326−12339.
(30) Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635−1643. This compound has been reported as a cis/trans mixture.
(31) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965.
(32) Goodfellow, V. S.; Marathe, M. V.; Whalley, E. T.; Fitzpatrick, T. D.; Kuhlman, K. G. Preparation of bradykinin antagonist peptides incorporating N-substituted glycines. *PCT Int. Appl.* WO 9524422,1995, p 22.
(33) Huang, L.; Zhang, Y.; Staples, R. J.; Huang, R. H.; Wulff, W. D. *Chem.—Eur. J.* **2012**, *18*, 5302−5313.
(34) Simoneau, B.; Lavallee, P.; Anderson, P. C.; Bailey, M.; Bantle, G.; Berthiaume, S.; Chabot, C.; Fazal, G.; Halmos, T.; Ogilvie, W. W.; Poupart, M.-A.; Thavonekham, B.; Xin, Z.; Thibeault, D.; Bolger, G.; Panzenbeck, M.; Winquist, R.; Jung, G. L. *Bioorg. Med. Chem.* **1999**, *7*, 489−508.
(35) Concellón, J. M.; Rodríguez-Solla, H.; Simal, C. *Adv. Synth. Catal.* **2009**, *351*, 1238−1242. The reported spectrum data for the compound **3c** in this reference does not match our data or the structure of **3c**.
(36) Huynh, T. H. V.; Shim, I.; Bohr, H.; Abrahamsen, B.; Nielsen, B.; Jensen, A. A.; Bunch, L. *J. Med. Chem.* **2012**, *55*, 5403−5412.
(37) Kouzo, S.; Tatsuya, Z.; Takeshi, T.; Yoshimasa, I.; Hiroki, F.; Satoru, K.; Jun, M.; Junko, W.; Hiroshi, I.; Nobuaki, T. N-aryl amide compounds and related compounds as ROCK inhibitors and their preparation, pharmaceutical compositions and use in the treatment of ROCK-related diseases. *PCT Int. Appl.* WO 2007/026920, 2007.
(38) Ishihara, K.; Hanaki, N.; Funahashi, M.; Miyata, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1721−1730.
(39) Fumeaux, R.; Menozzi-Smarrito, C.; Stalmach, A.; Munari, C.; Kraehenbuehl, K.; Steiling, H.; Crozier, A.; Williamson, G.; Barron, D. *Org. Biomol. Chem.* **2010**, *8*, 5199−5211.
(40) Solladié-Cavallo, A.; Simon-Wermeister, M.-C.; Farkhani, D. *Helv. Chim. Acta* **1991**, *74*, 390−396.
(41) For examples in the literature on the synthesis of L-DOPA, see (a) Sayyed, I. A.; Sudalai, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3111−3116. (b) Valdés, R. H.; Puzer, L.; Gomes, M., Jr.; Marques, C. E. S. J.; Aranda, D. A. G.; Bastos, M. L.; Gemal, A. L.; Antunes, O. A. C. *Catal. Commun.* **2004**, *5*, 631−634.