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Featured Article

Synthesis of Aminomethylene-*gem*-bisphosphonates Containing an Aziridine Motif: Studies of the Reaction Scope and Insight into the Mechanism

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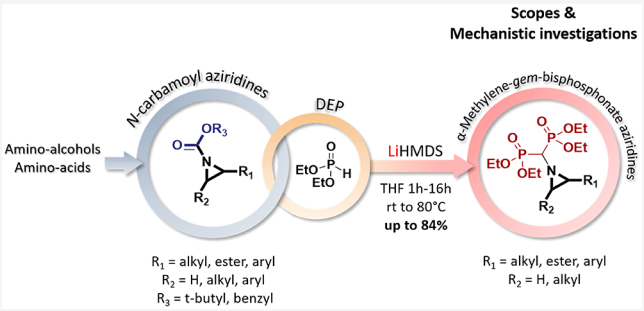
ABSTRACT: A broad range of *N*-carbamoylaziridines were obtained and then treated by the diethyl phosphonate anion to afford α-methylene-*gem*-bisphosphonate aziridines. Study of the reaction's scope and additional experiments indicates that the transformation proceeds via a new mechanism involving the chelation of lithium ion. This last step is crucial for the reaction to occur and disfavors the aziridine ring-opening. A phosphonate−phosphate rearrangement from a α-hydroxybisphosphonate aziridine intermediate is also proposed for the first time. This reaction provides a simple and convenient method for the synthesis of a highly functionalized phosphonylated aziridine motif.



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INTRODUCTION

Aziridines are widely studied as key intermediates in organic syntheses and represent a valuable source of chiral centers because of their regio- and stereoselectivity in ring-opening reactions. Their reactivity has recently been reviewed.[1] When combined with a phosphonate moiety (widely used in medicinal chemistry as a bioisoster of organic phosphate and insensitive to enzymatic cleavage), they are useful building blocks for the synthesis of aminophosphonates that can be considered as analogues of α-amino acids. For example, the synthesis of aziridine-2-phosphonates and aziridin-1-yl methylphosphonates have been well described in the literature.[2−5] However, the association of a chiral aziridine with several phosphonate groups is rather limited and may lead to promising scaffolds for obtaining biomolecules of interest. Indeed, bisphosphonates (or BPs, Figure 1) have been developed for their coordination abilities and their structural analogy with inorganic pyrophosphate (the P−C−P bridge replacing the P−O−P bonds is not sensitive to enzymatic cleavage), making them suitable for the treatment of bone diseases or drug delivery.[6−11] N-BPs are nitrogen-containing bisphosphonates, targeting enzymes of the mevalonate pathway and exhibiting antiosteoporosis and antiproliferative activities.[12,13] For example, the incadronate (Figure 1) is an antiosteoporosis drug with a 1-aminobisphosphonate motif.

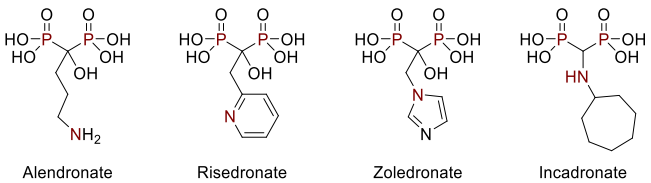

Figure 1. Structures of BPs and N-BPs clinically used or of biological interest.

Syntheses of 1-aminobisphosphonates (or aminomethylene-*gem*-bisphosphonates) are described through numerous methods,[14] namely the condensation of ethyl orthoformates and phosphites,[15,16] the Beckmann rearrangement of oximes,[17,18] or the bisphosphorylation of amides,[19,20] imines,[21] isonitriles,[22−24] or nitriles.[25] To our knowledge, such derivatives when containing an aziridine motif are not reported in the literature. Thus, we propose an original synthetic route involving lithiated diethylphosphite for the valorization of these three-membered rings in phosphorus chemistry (Scheme 1). We use *N*-carbamoylaziridines as starting material for the preparation of brand new phosphonylaziridine compounds, such as aziridine α-methylene-*gem*-bisphosphonates (abbreviated AzbisPs). To investigate the scope and limitations of the method, a library of *N*-carbamoylaziridines is obtained beforehand. In addition, complementary experiments are performed to propose a mechanism for the formation of such derivatives.

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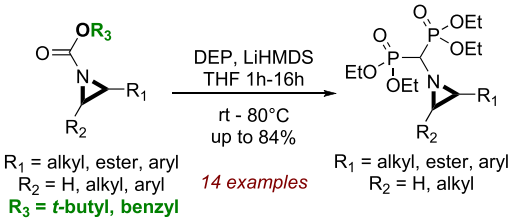
Scheme 1. Synthesis of Aziridine α-Methylene-*gem*-bisphosphonates (AzbisPs) from *N*-Carbamoylaziridines



RESULTS AND DISCUSSION

In the course of a medicinal project, we envisaged the preparation of β-aminophosphonates through the ring-opening of aziridines with phosphites,[26] a methodology poorly reported in the literature.[27,28] When such conditions (DEP/LiHMDS in THF) are applied to an *N*-Cbz-aziridine as substrate, we observed the formation of an aziridine α-methylene-*gem*-bisphosphonate (AzbisP) instead of the expected ring-opened product. To study the scope of this reaction, we examined the behavior of several *N*-Boc- or *N*-Cbz-protected aziridines.

With this aim, 14 substrates (Table 1, compounds **2a**−**n**) were synthesized starting from commercially available amino acids and amino alcohols through protection/reduction steps and then cyclization. Among them, nine *N*-carbamoylaziridines (**2a**, **2d**, **2e**, **2f**, **2g**, **2i**, **2j**, **2l**, and **2n**) were hitherto unknown compounds that may be viewed as valuable building blocks. According to the nature of the substituents, either Mitsunobu conditions (route A) or intramolecular substitution (route B) is used. Likely due to interactions/steric hindrance between the tosylate group and the phenyl moiety of the Cbz protecting group, the one-pot cyclization of *N*-Cbz-aziridines usually led to lower yields than under Mitsunobu conditions. Except in the case of the cyclohexyl aziridine **2k** (Table 1, entry 11), where the 3D conformation of the carbocycle is supposed to reduce the possible interactions between the two groups. We observed lower yields for compounds **2l** and **2m** (obtained as invertomers because of the high-energy barrier of the nitrogen inversion), and this may be associated with the formation of a highly constrained aziridine ring. In the Mitsunobu conditions, no reactivity is observed.

Having established the suitable reaction conditions (data not shown), aziridines **2a**−**n** were treated with 6.1 equiv of diethyl phosphite and 6 equiv of LiHMDS (1 M in THF), in anhydrous THF, at −78 °C. Then the reaction mixture was heated at the indicated temperature until completion of the reaction (TLC monitoring). According to our results, formation of AzbisPs occurs both in the presence of *N*-Boc and *N*-Cbz protecting groups, with an enhanced reactivity of the latter (Table 2, comparison between substrates **2b** and **2c**, **2i**, and **2j**). Three substrates did not lead to the expected derivatives. For the bicyclic compounds **2l** and **2m**, the lack of reactivity is mostly associated with the highly constrained conformation of the aziridine-ring, and the reduced product **3l** is isolated in high yields. For the biaryl aziridine **2n**, the starting material is almost entirely recovered even after 4 days at reflux. Thus, the high steric hindrance of the heterocycle appears to prevent the formation of the AzbisP derivative.

Ring-opened products are observed as byproducts for a few aziridines (**2f**, **2h** and **2i**), highlighting the competition between the formation of aziridine α-methylene-*gem*-bisphosphonates and β-aminophosphonates in the presence of an electron-withdrawing substituent, which enhances the electrophilicity of the aziridine ring. In the case of aryl or alkyl substituents, no byproducts are isolated.

As expected, we obtained better yields at higher temperatures (from rt to 55 °C) for derivatives **3b** and **3f**, whereas some aziridines (**2a**, **2c**, and **2k**) appeared unstable upon heating. Temperature has also an effect on the competition between ring-opening and AzbisP formation (no byproduct is isolated from **2f** after refluxing the reaction mixture at 80 °C, whereas the ring-opened product is recovered, in 5% and 16% yield, respectively, at room temperature and 50 °C) indicating that the AzbisP is the thermodynamic product of the reaction. In addition, the studied reaction does not lead to the epimerization of the aziridine ring, since compound **3g** is not isolated as a mixture of diastereoisomers.

The reaction does not occur on *N*-Boc-protected primary amines (Table 2, side chain of the lysine derivatives **2i** and **2j**). This difference of reactivity may be explained by the pK_{aH} values of aziridine and aliphatic amine (7−8 vs 9−11 in H_2O, respectively), which has an impact on the electrophilicity of the carbonyl moiety. The *N*-carbamoylaziridine moiety is more reactive in our conditions, thus allowing the selective formation of the AzbisP, even in the presence of another carbamate group. To validate this hypothesis, we examined the behavior of few analogues of the *N*-carbamoylaziridine scaffold with higher pK_{aH} values, such as *N*-Cbz-azetidine (10−11), *N*-Cbz-pyrrolidine (10.8), and *N*-Cbz-piperidine (10) derivatives (pK_{aH} values have been estimated using the MarvinSketch software),[33] as well as a well-known rearrangement product of *N*-carbamoylaziridines in the presence of azaphilic Lewis acids, the oxazolidine-2-one **4** (Scheme 2).[34] In all cases, the pK_{aH} of the nitrogen is higher than that of the aziridine scaffold, and no reactivity is observed in our conditions (DEP/LiHMDS).

The structures of bisphosphonate esters (compounds **3a**,**b**, **3d**−**i**, and **3k**) were readily identified by analysis of the NMR data, including bidimensional techniques, as well as mass spectrometry, and compared to their corresponding *N*-carbamoylaziridines used as starting materials (see the SI). In all cases, ^{1}H NMR spectra shows a triplet in the range of 2.4−2.8 ppm with a coupling constant value of ∼18 Hz and corresponding to a single proton. The 2D spectral data (COSY ^{1}H/^{1}H and HSQC ^{1}H/^{13}C) demonstrate that this proton is not coupling with other protons of the molecules and is associated with a carbon atom, whose signal is also a triplet at ∼65 ppm with a wide coupling constant of ∼150 Hz. This observation is consistent with the proposed structure including two phosphonate groups attached to the same carbon (P−CH−P). For example, a detailed study of the 1D and 2D NMR spectra (see the SI) for two AzbisPs (compounds **3d** and **3g**) and their corresponding *N*-carbamoylaziridines (compounds **2d** and **2g**) highlights the characteristic signals of these compounds and peak attribution. The aziridine structure is clearly recognizable by the presence of 2 doublets at ∼2 ppm in ^{1}H NMR (corresponding to the methylene of the aziridine ring) in the AzbisPs, which are also present in ^{1}H NMR spectrum of the starting material, supporting that the ring is kept intact at the end of the reaction. In addition, COSY and ^{13}C spectra also demonstrate the presence of the aziridine ring, the two doublets in ^{1}H NMR are associated with the same carbon according to HSQC experiments. The signal of the methylene protons is coupling only with the methyne proton of the aziridine ring in the COSY experiment.

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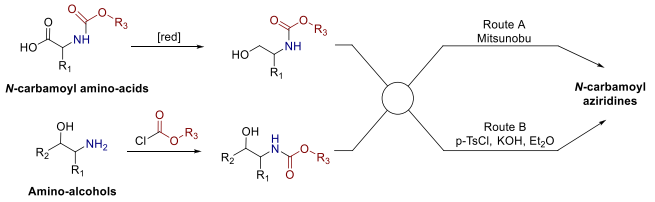
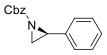
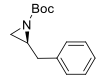
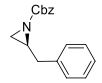
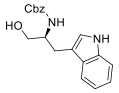
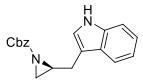
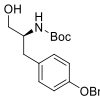
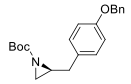
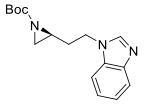
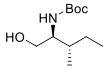
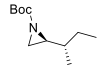
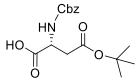
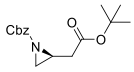
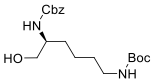
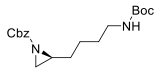
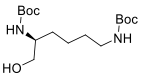
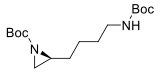
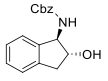
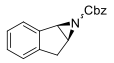
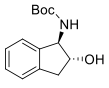
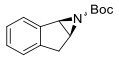
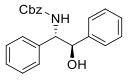
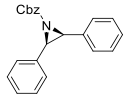
Table 1. Preparation of *N*-Carbamoylaziridines (as Substrates) from Commercially Available Amino Acids and Amino Alcohols



Entry	Starting Material		Synthetic route[a]	Product		Yield[b]
1	**1a**[c]		A		**2a**	76%
2	*N*-Boc-L-Phenylalaninol[d]		B		**2b**	75%
3	*N*-Cbz-L-Phenylalaninol[d]		A		**2c**	67%
4	**1d**[c]		A		**2d**	49%
5	**1e**[c]		A		**2e**	53%
6	L-Aspartic acid[d]		5 steps [29,c]		**2f**	22% (overall)
7	*N*-Boc-L-Isoleucinol[d]		B		**2g**	97%
8	Cbz-L-Asp(OtBu)-OH[d]		2 steps [30,31]		**2h**	37% (overall)
9	**1i**[c]		A		**2i**	95%
10	**1j**[c]		B		**2j**	Quantitative
11	**1k**[c]		B		**2k**[32]	97%
12	**1l**[c]		B		**2l**	16%
13	**1m**[c]		B		**2m**	31%
14	**1n**[c]		A		**2n**	76%

[a]Reaction conditions: Mitsunobu (route A) PPh_3, DEAD, THF, 0 °C to rt, overnight; one-pot cyclization (route B) *p*-TsCl, KOH, Et_2O, reflux, overnight. [b]Isolated yield after purification by column chromatography. [c]Preparation of starting material **1a**, **1d**, **1e**, and **1i**–**n** is available in the Experimental Section. [d]Commercially available.

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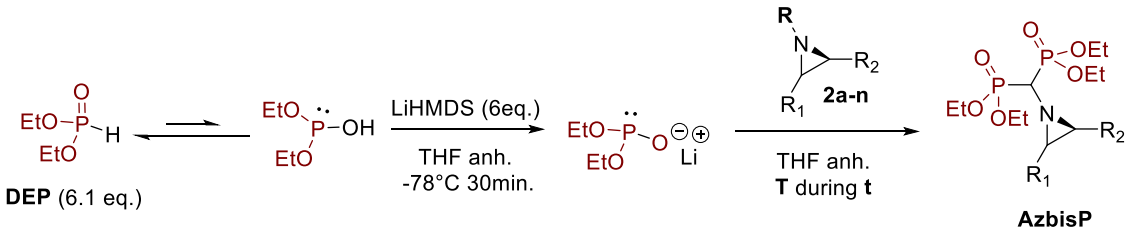
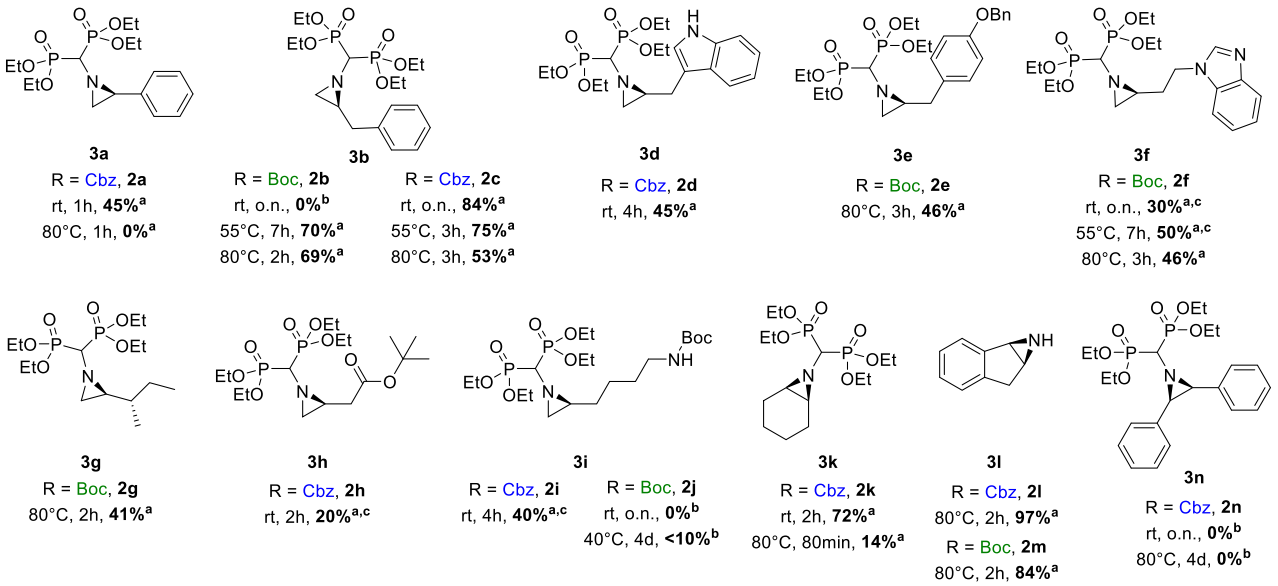
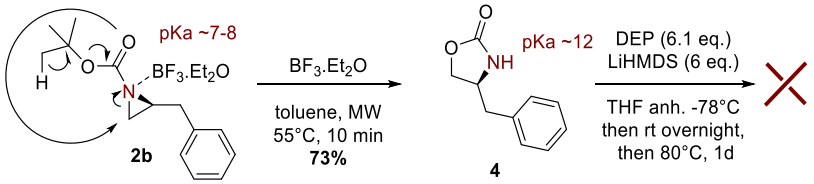
Table 2. Substrate Scope for the Formation of Aziridine α-Methylene-*gem*-bisphosphonates*





*Isolated yield after purification by column chromatography. Abbreviation o.n. means overnight. [a]Total conversion indicated by TLC. [b]Starting material recovered. [c]Corresponding ring-opened byproduct was also isolated (from **2f**, 5% at rt and 16% at 55 °C) or detected (from **2h** and **2i**).

Scheme 2. Synthesis of the Oxazolidine-2-one 4 from 2b Using a Previously Published Procedure[34] and Its Lack of Reactivity toward Nucleophilic Attack of Diethylphosphite[a]



[a]The chelation model and the proposed mechanism for the ring expansion of N-Boc-aziridines into oxazolines catalyzed by azaphilic Lewis acids is well-known in the literature.[35,36].

We then became interested in deciphering the mechanism of the reaction. Because the aziridine **2g** does not show any epimerization, we exclude the ring opening of the aziridine and its subsequent ring closing. Thus, our first hypothesis consisted in the nucleophilic attack of 1 equiv of diethyl phosphite anion on the carbonyl group, leading to the elimination of the alkoxide and the formation of an aziridine *N*-carbamoyl phosphonate (Scheme 3A). Differences of reactivity between *N*-Boc and *N*-Cbz substrates support this assumption as the benzyl oxide ion may be considered as a better leaving group than the *tert*-butyl oxide one. This kind of addition/elimination occurring on a carbamate moiety has already been reported in the literature.[37] In addition, an acyl derivative of the 2-benzylaziridine treated in our conditions (data not shown) did not lead to the formation of the corresponding AzbisP, which indicated the key role of the carbamoyl moiety.

This addition/elimination step may be competing with the nucleophilic attack on the aziridine ring that is also an electrophilic center. Here, we assumed that the chelation of the lithium with the ester moiety enhanced the reactivity of the carbamate, since lithium is considered as a better Lewis acid than the other alkali ions (sodium and potassium). Corresponding models and rules are presented in Scheme 3A. Herein, we propose a different site of chelation for the Lewis acid (than the one drawn in Scheme 2) on the basis of the work of Lectka et al.,[36] indicating that coordination to the carbonyl may be better at activating the substrate toward external nucleophilic attack.

In a second step, the *N*-carbamoyl phosphonate intermediate may be subject to a second nucleophilic attack of the diethyl phosphite anion affording an α-hydroxybisphosphonate derivative as a second intermediate (Scheme 3B). This scaffold is known to undergo [1,2]-phospha-Brook rearrangement

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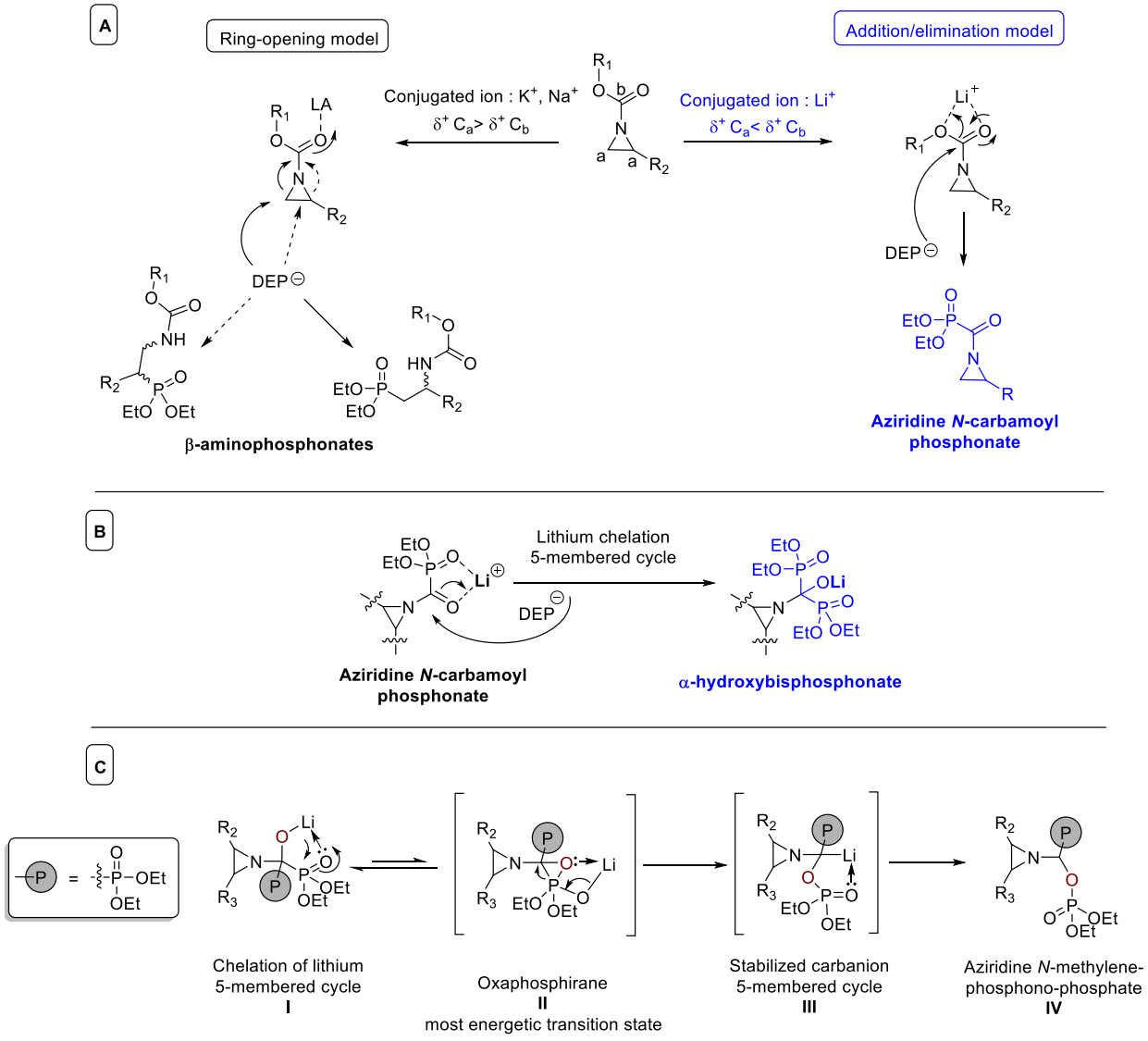
Scheme 3. Mechanistic Investigation. (A) Models for the Ring Opening of *N*-Carbamates Compared with the Addition of DEP on the Carbamate Moiety in the Presence of Lithium Cations. (B) Second Nucleophilic Attack Leading to a Hypothetic *α*-Hydroxybisphosphonate Intermediate. (C) [1,2]-Phospha-Brook Rearrangement with Lithiated Base Starting from *α*-Hydroxybisphosphonate Intermediate



(phosphonate−phosphate rearrangement) in the presence of a base, leading to the formation of a phosphate moiety (Scheme 3C).[38−44]

The proposed mechanism (Scheme 3C) is adapted from the work of Ranga et al.,[45] who studied the *n*-BuLi-mediated [1,2]-phospha-Brook rearrangement and the addition of lithiated diethyl phosphite on acetophenone. Their conclusions (supported by DFT calculations and ^{31}P NMR experiments) proved the crucial role of lithium in the stabilization of the transition states. This rearrangement occurs right after the formation of the intermediate **I** (Scheme 3C). The lithium, conjugated to the hydroxylate, chelates the phosphonate and induces the addition of the hydroxyl anion on the phosphorus atom, leading to the formation of the oxaphosphirane high energy intermediate **II**. The cleavage of the P−C bond of the lithium-chelated oxaphosphirane and the subsequent creation of the P−O bond then forms the 5-membered carbanion containing cycle intermediate **III**. The rearrangement presumably proceeds through lithium−proton exchange (involving the diethyl phosphite as supposed by Ranga et al.).

To go further in the study of the impact of the lithium ion in the proposed mechanism and rearrangement as well as the nature of the base, we envisaged additional experiments (Table 3). Thus, various bases susceptible to deprotonate the diethyl phosphite were tested using aziridine **2f** as substrate. In the presence of *t*BuOK (entry 1), only 3% of AzbisP was

Table 3. Influence of the Nature of the Base on the Formation of AzbisPs

			yield (%)	
entry	base (6 equiv)	pK_a	AzbisP 3f (%)	*β*-aminoP (%)
1	*t*BuOK	17	3	**47**
2	NaHMDS	30	0	9
3	**LiHMDS**	30	**30**	5
4	NaH	35	0	5

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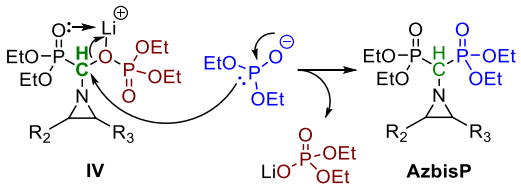
recovered, and we mainly observed the formation of ring-opened product (47% yield). When using NaHMDS (entry 2) or LiHMDS (entry 3) with similar pK_a values, no AzbisP is observed for NaHMDS and only 9% of the ring-opened product is recovered. These results are in agreement with previous data from the literature, comparing the effect of various [M]HMDS bases on the double addition of DEP on acid chlorides[39] and the recent mechanistic study of the role of the lithium ion in the [1,2]-phospha-Brook rearrangement.[45] When a stronger base such as NaH was used (entry 4), only traces of ring-opened product were observed.

Accordingly, the lithium is conjugated to the hydroxylate anion generated after the second nucleophilic attack of DEP on the acylphosphonate moiety (Scheme 3C). Lithium acts as a Lewis acid as well as a conjugated cation. It is supposed to chelate the phosphonate group **I** to facilitate the formation of the oxaphosphirane **II** and to stabilize the carbanion **III** with the formation of a strong ion pair. The proposed model (Scheme 3B) is hypothesized from the mechanism of the reverse reaction, the phosphate−phosphonate rearrangement, in the presence of strong lithiated base,[46,47] and on the basis of the work of Ranga et al.[45] This point further reinforces the crucial role of lithium in the stabilization of the transition states. The [1,2]-phospha-Brook rearrangement likely ends by the lithium−proton exchange between DEP and the transition state **III**.

In the last step, we assumed that the newly formed phosphate group may be substituted by a third equivalent of deprotonated diethyl phosphite, still with the assistance of the lithium as a Lewis acid, which chelates the phosphate group and leads to the AzbisP product (Scheme 4). A similar

Scheme 4. Substitution of the phosphate Group by a Third Nucleophilic Attack of DEP



substitution reaction is observed by Fitch and Moedritzer on a phosphonyl phosphate compound in the presence of PCl_5.[48] It has to be specified that the diethyl phosphoester moiety (in red, intermediate IV, Scheme 4), as well as the phosphonate group, certainly increase the electrophilicity of the vicinal carbon atom (in green, intermediate IV, Scheme 4), assisting consequently the nucleophilic attack of DEP (in blue, Scheme 4) on this position. As for the previous steps, the aziridine ring is supposed to participate in the same way because of the low pK_a value of its nitrogen atom. This last step is thought to be fast, in order to consume quickly the rearranged phosphorylated compound and thus preventing the reverse reaction.

Furthermore, several attempts to isolate intermediates during the reaction and to synthesize the *N*-carbamoyl phosphonate intermediates were unsuccessful, thus demonstrating both high reactivity and instability of these species. When using lower equivalents of DEP/base (Table 4), total consumption of the starting *N*-carbamoylaziridine is observed but the yields of the recovered AzbisP remain below the one obtained with 6 equiv of DEP/LiHMDS, and yet no intermediate is isolated. The similar yields obtained for 2

Table 4. Influence of the Amounts of DEP/LiHMDS on the Yield of the Reaction

entry	DEP (equiv)	LiHMDS (equiv)	time (h)	yield of **3b** (%)
1	**2.1**	2	6	**13**
2	**3.1**	3	4.5	**14**
3	4.1	4	4	29
4	5.1	5	2.5	32
5	**6.1**	6	2	**69**

and 3 equiv of the reactants (Table 4, entry 1 and 2) may suggest that the reaction requires at least 3 equiv of DEP/LiHMDS to be in stoichiometric conditions.

CONCLUSION

N-Carbamoylaziridines are efficiently converted into their corresponding methylene-*gem*-bisphosphonylated derivatives in the presence of LiHMDS and DEP. To our knowledge, it is the first time that such reaction has been reported in the literature. This transformation preferably occurs with *N*-Cbz-aziridines and competes with the aziridine ring-opening reaction. A broad range of *N*-Cbz- and *N*-Boc-aziridines were synthesized to study the scope of the reaction and afforded the desired phosphonylated compounds with mild to good yield. Influence of the nature of the base, the nature of the aziridine protecting group, amount of reactants, and the aziridine substituent were studied.

According to the reaction scope and additional experiments, we proposed a mechanism and highlighted the essentiality of the lithium ion and the basicity of the nitrogen. The latter involved a phosphonate−phosphate rearrangement newly described from a lithiated α-hydroxybisphosphonate species.

EXPERIMENTAL SECTION

General Information. Reagents were from the followed suppliers: Sigma-Aldrich, Alfa Aesar, Acros, or TCI. Anhydrous solvents (sealed flasks and stored on molecular sieves) were from Sigma-Aldrich (acetonitrile, MeOH, dichloromethane, THF, DMF, Et_2O) or distilled beforehand on P_2O_5 or $CaCl_2$ (dichloromethane) or sodium and benzophenone (THF), according to protocols by Armarego and Perrin.[49] Diethyl phosphite (Acros) was distilled on KOH under reduced pressure and stored in a sealed round-bottom flask under argon atmosphere and in the dark. Reactions that required heating were performed in hot plate/heating block apparatus with internal temperature control.

Microwave conditions reactions were performed on an Anton-Paar Monowave instrument and using sealed tubes; the reaction temperature was monitored by external surface sensor.

Thin-layer chromatography (TLC) was performed on precoated aluminum sheets of silica 60 F254 (Merck, Art. 5554). Visualization of products was accomplished by UV absorbance (254 nm) and/or by charring with Ninhydrin solution, "Molybden blue", or sulfuric acid 5% (v/v) in ethanol. Flash chromatography on silica gel were performed on the automated system Biotage Isolera 4 and silica cartridges (Buchi Flashpure Silica or Biotage ZIP Si Cartridge).

NMR spectra were recorded in the Laboratoire de Mesures Physiques (LMP, University of Montpellier) on Brüker Avance spectrometers (400, 500, or 600 MHz for ^{1}H NMR spectra, 101 or 126 MHz for ^{13}C NMR spectra, and 162 or 202 MHz for ^{31}P NMR), at room temperature (20 °C). Chemical shifts were reported in ppm (parts per million) and determined according to the solvent peak used as internal reference and relatively to the trimethylsilyl peak (TMS) for ^{1}H and ^{13}C NMR and according to an external reference for ^{31}P NMR. Used solvents were $CDCl_3$, D_2O, MeOD-d_4, and DSMO-d_6 (Sigma-Aldrich). COSY (^{1}H 2D), HSQC ^{1}H−^{13}C, and HMBC ^{1}H−^{13}C were obtained to interpret and confirm ^{1}H and ^{13}C NMR

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spectra. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constants and integration. High-resolution mass spectra (HRMS) were recorded on a Q-TOF Synapt-G2-S instrument using electrospray ionization (ESI) in positive or negative ion polarity mode.

The pK_a and pK_{aH} values calculations were performed on Marvin Sketch software (ChemAxon, version 19.13.00)[33] from the compound structures. The acidic pK_a value was leveled up to 50 for the calculations.

General Procedure for the Preparation of *N*-Boc- and *N*-Cbz-aziridines Using the Mitsunobu Reaction (Table 1, Route A). *N*-Cbz- or *N*-Boc-amino alcohol (1.0 equiv) was dissolved under argon atmosphere in anhydrous THF (13.2 mL/mmol) at 0 °C. Triphenylphosphine (1.5 equiv) was added in one portion, followed by diethyl azodicarboxylate (1.64 equiv) dropwise, at 0 °C. The reaction mixture was allowed to warm to room temperature and kept stirring until completion of the reaction (TLC monitoring). Solvents were removed in vacuum, and the crude was purified by silica gel flash chromatography (petroleum ether/ethyl acetate) to obtain the desired compound.

*Benzyl (S)-2-Phenylaziridine-1-carboxylate (**2a**).* The compound (*S*)-**2a** (1.42 g, 5.61 mmol, 76% yield) was obtained as an oil following the procedure described above (overnight reaction) from compound **1a** (2.00 g, 7.38 mmol). R_f petroleum ether/EtOAc (7/3, v/v): 0.90. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.13 (m, 10H, HAr), 5.07 (q, J = 12.3 Hz, 2H, CH_2Ph), 3.42 (dd, J = 6.3, 3.6 Hz, 1H, CH), 2.63 (d, J = 6.3 Hz, 1H, CH_2CH), 2.22 (d, J = 3.6 Hz, 1H, CH_2CH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.2 (s, C(O)Cbz), 137.0 (s, CAr), 135.8 (s, CAr), 129.0−127.8 (m, CHAr), 126.3 (s, CHAr), 68.5 (s, CH_2Ph), 39.5 (s, CH), 35.3 (s, CH_2CH). HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{16}NO_2$ 254.1181, found 254.1181.

*Benzyl (S)-2-Benzylaziridine-1-carboxylate (**2c**).* The compound (*S*)-**2c** (626 mg, 2.34 mmol, 67% yield) was obtained as a white solid following the procedure described above (overnight stirring) from commercially available *N*-Cbz-L-phenylalanilol (1.00 g, 3.50 mmol). R_f hexane/EtOAc (7/3, v/v): 0.80. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.19 (m, 10H, CHAr), 5.12 (s, 2H, OCH_2Ph), 3.04−2.90 (m, 1H, $CHCH_2$Ph), 2.77−2.64 (m, 2H, CHAz, $CHCH_2$Ph), 2.39 (d, J = 5.9 Hz, 1H, CH_2, Az), 2.10 (d, J = 3.5 Hz, 1H, CH_2, Az). Data in accordance with the literature.[50]

*Benzyl (S)-2-((1H-Indol-3-yl)methyl)aziridine-1-carboxylate (**2d**).* The compound (*S*)-**2d** (550 mg, 1.80 mmol, 49% yield) was obtained as an oil following the procedure described above (overnight stirring) from compound **1d** (1.20 g, 3.70 mmol). R_f petroleum ether/EtOAc (7/3, v/v): 0.43. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H, NH), 7.58 (dd, J = 7.9, 0.8 Hz, 1H), 7.41−7.28 (m, 7H, CHAr), 7.22−7.18 (m, 1H, CHAr), 7.16−7.09 (m, 1H, CHAr), 5.13 (s, 2H, OCH_2Ph), 3.14−3.04 (m, 1H, $CHCH_2$C), 2.90 (ddd, J = 15.3, 5.8, 0.7 Hz, 1H, $CHCH_2$C), 2.82 (qd, J = 5.9, 3.8 Hz, 1H, CHAz), 2.40 (d, J = 6.0 Hz, 1H, CH_2, Az), 2.14 (d, J = 3.7 Hz, 1H, CH_2, Az). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.3 (s, C(O)Boc), 163.5 (s, CAr), 136.0 (s, CAr), 129.8−126.6 (m, CHAr), 122.3 (d, J = 16.6 Hz, CHAr), 119.6 (s, CHAr), 118.9 (s, CHAr), 112.2 (s, CHAr), 111.3 (s, CHAr), 68.2 (s, OCH_2Ph), 38.3 (s, CHAz), 32.0 (s, CH_2, Az), 28.2 (s, $CHCH_2$C). HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1446.

*tert-Butyl (S)-2-(4-(Benzyloxy)benzyl)aziridine-1-carboxylate (**2e**).* The compound (*S*)-**2e** (766 mg, 2.26 mmol, 53% yield) was obtained as an oil following the procedure described above (6h stirring) from compound **1e** (1.51 g, 4.23 mmol). R_f petroleum ether/EtOAc (9/1, v/v): 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45−7.41 (m, 2H, CHAr), 7.41−7.35 (m, 2H, CHAr), 7.35−7.29 (m, 1H, CHAr), 7.24−7.20 (m, 2H, CHAr), 6.95−6.90 (m, 2H, CHAr), 5.05 (s, 2H, OCH_2Ph), 2.97−2.82 (m, 1H, $CHCH_2$Ph), 2.66−2.53 (m, 2H, $CHCH_2$Ph, CHAz), 2.29 (d, J = 5.9 Hz, 1H, CH_2, Az), 2.01 (d, J = 3.4 Hz, 1H, CH_2, Az), 1.44 (s, 9H, CH_3, Boc). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.6 (s, C(O)Boc), 157.7 (s, CAr), 137.3 (s, CAr), 131.3−126.7 (m, 9C, CHAr, CAr), 115.0 (s, CHAr), 81.2 (s, $\underline{C}(CH_3)_3$, Boc), 70.2 (s, OCH_2Ph), 38.7 (s, CHAz), 37.7 (s, $CHCH_2$Ph), 31.5 (s, CH_2, Az), 28.1 (s, 3C, CH_3, Boc). HRMS (ESI/Q-TOF) m/z: [M-H]$^-$ calcd for $C_{21}H_{24}NO_3$ 338.1756, found 338.1753.

*Benzyl (S)-2-(4-((tert-Butoxycarbonyl)amino)butyl)aziridine-1-carboxylate (**2i**).* The compound (*S*)-**2i** (900 mg, 2.59 mmol, 95% yield) was obtained as an oil following the procedure described above (overnight stirring) from compound **1i** (1.00 g, 2.73 mmol). R_f petroleum ether/EtOAc (7/3, v/v): 0.51. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38−7.30 (m, 5H, CHAr), 5.12 (s, 2H, OCH_2Ph), 4.49 (s, 1H, NH), 3.10 (m, 2H, CH_2NH), 2.46−2.38 (m, 1H, CHAz), 2.34 (d, J = 6.1 Hz, 1H, CH_2, Az), 1.98 (d, J = 3.8 Hz, 1H, CH_2, Az), 1.55−1.45 (m, 6H, $3CH_2$), 1.44 (s, 9H, $3CH_3$, Boc). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 163.6 (s, C(O)Cbz), 156.1 (s, C(O)Boc), 136.0 (s, CAr), 128.7 (s, CHAr), 128.5 (s, CHAr), 128.3 (s, CHAr), 68.2 (s, OCH_2Ph), 40.6 (s, CH_2NH), 38.3 (s, CHAz), 32.0 (s, CH_2, Az), 31.9 (s, CH_2), 28.6 (s, 3C, $3CH_3$, Boc), 24.2 (s, 2C, CH_2). HRMS (ESI/Q-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{28}N_2O_4Na$ 371.1947, found 371.1945.

*Benzyl (2S,3S)-2,3-Diphenylaziridine-1-carboxylate (**2n**).* The compound (*S*)-**2n** (724 mg, 2.20 mmol, 76% yield) was obtained as an oil following the procedure described above (overnight stirring) from compound **1n** (1.00 g, 2.88 mmol). R_f petroleum ether/EtOAc (7/3, v/v): 0.90. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29−7.15 (m, 13H, CHAr), 6.94 (dd, J = 7.8, 1.6 Hz, 2H, CHAr), 4.91 (dd, J = 65.4, 12.1 Hz, 2H, OCH_2Ph), 3.71 (s, 2H, CHAz). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 160.5 (s, C(O)Cbz), 135.5 (s, CAr), 129.7−125.5 (m, CHAr), 68.3 (s, OCH_2Ph), 48.5 (s, CHAz). HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{20}NO_2$ 330.1494, found 330.1491.

General Procedure for the Preparation of *N*-Boc- and *N*-Cbz-aziridines from Amino Alcohols via One-Pot Cyclization (Table 1, Route B). *N*-Cbz- or *N*-Boc-amino alcohol (1 equiv) was dissolved under argon atmosphere in anhydrous diethyl ether (15 mL/mmol) at room temperature. Dry *p*-toluenesulfonyl chloride (2.2 equiv) was added, followed by the addition of KOH grinded pellets (9.0 equiv). A drying tube filled with calcium chloride ($CaCl_2$) sealed the condenser. The reaction mixture was heated to 40 °C and stirred until completion of the reaction. Solvents were evaporated in vacuum, and the crude was dissolved in ethyl acetate. The salts were filtered, and the filtrate was concentrated to obtain the desired compound. The purification step using silica gel flash chromatography (petroleum ether/ethyl acetate gradient) was only performed for compounds **2b**, **2l**, and **2m**.

*tert-Butyl (S)-2-Benzylaziridine-1-carboxylate (**2b**).* The compound (S)-**2b** (1.39 g, 5.96 mmol, 75% yield) was obtained as a pale orange oil following the procedure described above (overnight stirring) from commercially available *N*-Boc-L-phenylalanilol (2.00 g, 7.96 mmol). R_f petroleum ether/EtOAc (9/1, v/v): 0.75. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.29 (m, 4H, CHAr), 7.23 (dt, J = 5.5, 4.2 Hz, 1H, CHAr), 2.96 (dd, J = 14.0, 5.4 Hz, 1H, CH_2Ph), 2.66 (dd, J = 18.9, 4.8 Hz, 1H, CH_2Ph), 2.66−2.60 (m, 1H, CHAz), 2.31 (d, J = 5.7 Hz, 1H, CH_2, Az), 2.03 (d, J = 3.5 Hz, 1H, CH_2, Az), 1.44 (s, 9H, $3CH_3$, Boc). Data in accordance with the literature.[51]

*tert-Butyl (S)-2-((S)-sec-Butyl)aziridine-1-carboxylate (**2g**).* The compound (*S*)-**2g** (891 mg, 4.47 mmol, 97% yield) was obtained as an oil following the procedure described above (overnight stirring) from commercially available *N*-Boc-L-isoleucinol (1.00 g, 4.60 mmol). R_f hexane/EtOAc (7/3, v/v): 0.85. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.22 (d, J = 6.3 Hz, 1H, CH_2, Az), 2.18−2.14 (m, 1H, CHAz), 1.90 (d, J = 3.9 Hz, 1H, CH_2, Az), 1.65 (tdd, J = 14.5, 7.3, 5.0 Hz, 1H, CH_2CH_3), 1.44 (s, 9H, $3CH_3$, Boc), 1.41−1.32 (m, 1H, CH_2CH_3), 1.17−1.09 (m, 1H, $CHCH_3$), 0.97 (t, J = 7.5 Hz, 3H, CH_3CH_2), 0.91 (d, J = 6.8 Hz, 3H, CH_3CH). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 163.0 (s, C(O)Boc), 80.9 (s, $C(CH_3)_3$, Boc), 43.5 (s, CHAz), 37.8 (s, $CHCH_3$), 30.7 (s, CH_2, Az), 28.1 (s, 3C, $3CH_3$, Boc), 27.7 (s, CH_2CH_3), 16.1 (s, CH_3CH), 11.1 (s, CH_3CH_2). HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{11}H_{22}NO_2$ 200.1645, found 200.1643.

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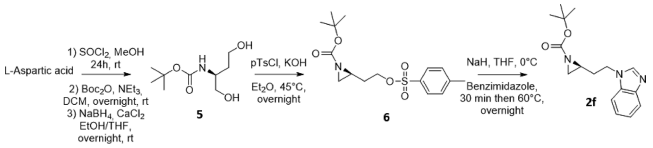
*tert-Butyl (S)-2-(4-((tert-Butoxycarbonyl)amino)butyl)aziridine-1-carboxylate (**2j**).* The compound (*S*)-**2j** (284 mg, 0.90 mmol, quantitative yield) was obtained as an oil following the procedure described above (4h stirring) from compound **1j** (300 mg, 0.90 mmol). R_f dichloromethane/MeOH (95/5, v/v): 0.70. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (s, 1H, NH), 3.12 (dd, J = 9.0, 4.2 Hz, 2H, CH_2NH), 2.34 (dt, J = 9.8, 4.9 Hz, 1H, CHAz), 2.25 (d, J = 6.1 Hz, 1H, CH_2, Az), 1.90 (d, J = 3.8 Hz, 1H, CH_2, Az), 1.53 (m, 6H, $3CH_2$), 1.45 (s, 9H, CH_3, Boc), 1.44 (s, 9H, CH_3, Boc). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 162.8 (s, C(O),Boc Az), 156.1 (s, C(O)Boc), 81.1 (s, $C(CH_3)_3$, Boc), 79.2 (s, $C(CH_3)_3$, Boc), 40.6 (s, CH_2NH), 38.0 (s, CHAz), 32.0 (s, CH_2), 31.8 (s, CH_2, Az), 28.6 (s, 3C, $3CH_3$, Boc), 28.1 (s, 3C, $3CH_3$, Boc), 24.3 (s, 2C, $2CH_2$). Weakly ionizable compound, molecular peak undetected in MS analysis, neither in positive or negative mode.

*Benzyl (1R,6S)-7-Azabicyclo[4.1.0]heptane-7-carboxylate (**2k**).* The compound (*S*)-**2k** (789 mg, 3.41 mmol, 97% yield) was obtained as a pale orange oil following the procedure described above (5h stirring) from compound **1k** (1 g, 3.5 mmol). R_f petroleum ether/EtOAc (9/1, v/v): 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.28 (m, 5H, CHAr), 5.12 (s, 2H, CH_2Ph), 2.71−2.59 (m, 2H, 2CHAz), 2.03−1.72 (m, 4H, $2CH_2$), 1.46−1.20 (m, 4H, $2CH_2$). Data in accordance with the literature.[32] Weakly ionizable compound, molecular peak undetected in MS analysis, neither in positive or negative mode.

*Benzyl (1aR,6aS)-6,6a-Dihydroindeno[1,2-b]azirine-1(1aH)-carboxylate (Invertomers) (**2l**).* The compound (*S*)-**2l** (150 mg, 0.57 mmol, 16% yield) was obtained as an oil following the procedure described above (overnight stirring) from compound **1l** (1.00 g, 3.53 mmol). R_f hexane/EtOAc (7/3, v/v): 0.30. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.31 (m, 8H, CHAr, A,B), 7.30−7.22 (m, 5H, CHAr, A,B), 5.15 (s, 0.68H, CH_2Ph, A), 5.13 (s, 2H, CH_2Ph, B), 5.10 (d, J = 2.9 Hz, 0.42H, CCHAz, A), 5.05 (d, J = 5.2 Hz, 1H, CCHAz, B), 4.45 (t, J = 9.5 Hz, 1H, $CHAzCH_2$, B), 4.06 (t, J = 6.7 Hz, 0.12H, $CHAzCH_2$, A), 3.34 (dd, J = 15.3, 8.2 Hz, 0.33H, CH_2, A), 3.26 (dd, J = 15.8, 7.2 Hz, 1H, CH_2, B), 2.90 (dd, J = 15.8, 7.3 Hz, 1H, CH_2, B), 2.72 (dd, J = 15.3, 9.1 Hz, 0.29H, CH_2, A). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1162.

*tert-Butyl (1aR,6aS)-6,6a-Dihydroindeno[1,2-b]azirine-1(1aH)-carboxylate (invertomers) (**2m**).* The compound (*S*)-**2m** (480 mg, 2.08 mmol, 31% yield) was obtained as an oil following the procedure described above (2 h stirring) from compound **1m** (1.67 g, 6.70 mmol). R_f hexane/EtOAc (7/3, v/v): 0.50. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, J = 7.3 Hz, 2H, CHAr, A,B), 7.32−7.19 (m, 4H, CHAr, A,B), 5.06 (d, J = 6.2 Hz, 0.42H, CCHAz, A), 5.04 (d, J = 5.2 Hz, 1H, CCHAz, B), 4.37 (s, 1H, $CHAzCH_2$, B), 4.08 (dd, J = 15.6, 7.9 Hz, 0.37H, $CHAzCH_2$, A), 3.30 (dd, J = 15.2, 8.2 Hz, 0.55H, CH_2, A), 3.23 (dd, J = 15.8, 7.3 Hz, 1H, CH_2, B), 2.87 (dd, J = 15.8, 7.2 Hz, 1H, CH_2, B), 2.69 (dd, J = 15.2, 9.1 Hz, 0.56H, CH_2, A), 1.48 (s, 5H, CH_3, Boc A), 1.47 (s, 9H, CH_3, Boc B). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 156.2 (s, C(O)Boc), 142.3 (s, CAr), 141.2 (s, CAr), 130.8−123.3 (m, CHAr), 82.1 (s, CCHAz, A), 75.0 (s, CCHAz, B), 62.0 (s, CH_2CHAz, A), 54.8 (s, CH_2CHAz, B), 37.0 (s, CH_2, B), 36.2 (s, CH_2, A), 28.5 (s, 3C, CH_3, Boc). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$ 232.1332, found 232.1329.

Synthesis of Aziridine 2f.



*tert-Butyl (S)-(1,4-Dihydroxybutan-2-yl)carbamate (**5**).* The protocol is adapted from the work of Jorrës et al.[29] Compound **5** was isolated as oil (6.54 g, 31.80 mmol, 73% yield) from L-aspartic acid. Data in accordance with the literature.[29]

*tert-Butyl (S)-2-(2-(Tosyloxy)ethyl)aziridine-1-carboxylate (**6**).* The procedure is adapted from the work of Aaseng et al.[52] The compound **5** (2.96 g, 14.40 mmol, 1 equiv) was dissolved in diethyl ether (15 mL/mmol) under argon atmosphere at room temperature. *p*-Toluenesulfonyl chloride (2.2 equiv) was added, followed by ground KOH pellets (6 equiv). The reaction mixture was then heated at 45 °C and kept under stirring overnight. Volatiles were removed in vacuo and purified by silica gel flash chromatography (petroleum ether/ethyl acetate gradient) to obtain the title compound as an oil (3.15 g, 9.23 mmol, 64% yield). R_f hexane/EtOAc (6/4, v/v): 0.65. $[\alpha]_D^{20}$ +23 (c 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 1H, HAr, Ts), 7.35 (d, J = 8.2 Hz, 1H, HAr, Ts), 4.23−4.14 (m, 2H, CH_2O), 2.45 (s, 3H, CH_3,Ts), 2.43−2.38 (m, 1H, CHAz), 2.26 (d, J = 6.5 Hz, 1H, CH_2, Az), 1.92 (d, J = 3.4 Hz, 1H, CH_2, Az), 1.90−1.84 (m, 1H, CH_2CH_2O), 1.79−1.72 (m, 1H, CH_2CH_2O), 1.42 (s, 9H, CH_3,Boc). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 161.1 (s, NC(O)O, Boc Az), 143.9 (s, CCH_3, Ts), 132.0 (s, CS, Ts), 128.9 (m, 2C, CH, Ts), 126.9 (m, 2C, CH, Ts), 80.4 (s, CCH_3, Boc), 67.0 (s, CH_2O), 33.3 (s, CHAz), 30.9 (s, CH_2CH_2N), 30.4 (s, CH_2, Az), 26.8 (s, 3C, CH_3,Boc), 20.6 (s, CH_3, Ts). HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{23}NO_5SNa$ 364.1195, found 364.1194.

*(S)-tert-Butyl 2-(2-(1H-Benzimidazol-1-yl)ethyl)aziridine-1-carboxylate (**2f**).* NaH (256 mg, 60% in oil, 1.2 equiv) was dissolved in anhydrous THF (4.76 mL/mmol of benzimidazole) at 0 °C, under argon atmosphere. Benzimidazole (760 mg, 6.44 mmol, 1.2 equiv) previously dissolved in anhydrous THF (2.38 mL/mmol of benzimidazole) was added, and the mixture was stirred for 30 min. The mixture was warmed to room temperature, and *N*-Boc-tosylated aziridine **6** (1.83 g, 5.36 mmol, 1 equiv) dissolved in anhydrous THF (3 mL/mmol of aziridine) was added. The mixture was then heated to 60 °C and kept under stirring overnight. Volatiles were removed in vacuo, and the crude was dissolved in ethyl acetate. After filtration (glass filter, porosity 4), the salts were washed with ethyl acetate and the filtrates were combined and concentrated then purified by flash chromatography on silica gel (petroleum ether/ethyl acetate gradient) to obtain the title compound as a colorless oil (750 mg, 2.61 mmol, 50% yield). Thus, compound **2f** was obtained in five steps with 22% overall yield from L-aspartic acid. R_f EtOAc: 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (s, 1H, NCHArN), 7.81 (dd, J = 6.7, 1.9 Hz, 1H, HAr), 7.43 (dd, J = 7.0, 2.1 Hz, 1HAr), 7.34−7.27 (m, 2H, HAr), 4.41 (dd, J = 7.8, 5.8 Hz, 2H, CH_2CH_2N), 2.36 (ddt, J = 8.3, 6.2, 3.8 Hz, 1H, CHN), 2.29 (d, J = 6.2 Hz, 1H, $CHCH_2N$), 2.27−2.20 (m, 1H, CH_2CH_2N), 1.91 (d, J = 3.6 Hz, 1H, $CHCH_2N$, Az), 1.72 (ddt, J = 14.3, 8.5, 5.8 Hz, 1H, CH_2CH_2N), 1.48 (s, 9H, $3CH_3$, Boc). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 162.22 (s, C(O), Boc), 144.2 (s, CAr), 143.5 (s, C-2), 133.7 (s, CAr), 123.1 (s, CAr), 122.3 (s, CAr), 120.7 (s, CAr), 109.7 (s, CAr), 81.9 (s, $C(CH_3)_3$,Boc), 43.1 (s, CH_2CH_2N), 35.2 (s, CHN), 32.8 (s, CH_2CH_2N), 31.8 (s, $CHCH_2N$), 28.1 (s, 3C, $3CH_3$, Boc). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}N_3O_2$ 288.1712, found 288.1718.

*Benzyl (R)-2-(2-(tert-Butoxy)-2-oxoethyl)aziridine-1-carboxylate (**2h**).* The procedure is adapted from the work of Jung et al.[30] Cbz-L-Asp(OtBu)-OH (882 mg, 2.73 mmol, 1 equiv) was dissolved in anhydrous THF (3.2 mL/mmol) under argon atmosphere, at 0 °C. BH_3·THF (1 M in THF, 5 equiv) was added portionwise. The mixture was stirred for 1 h at 0 °C and then allowed to warm at room temperature and quenched by slow addition of methanol. The mixture was concentrated in vacuo. The crude was purified on silica gel by flash chromatography (dichloromethane/ethyl acetate gradient) to obtain the amino alcohol[30] as an oil (508 mg, 1.64 mmol, 60% yield). For the next step, the protocol from Aaseng et al.[31] was adapted. The reduced compound (508 mg, 1.64 mmol, 1 equiv) was dissolved under argon atmosphere in anhydrous THF (13.2 mL/mmol) at 0 °C. Triphenylphosphine (1.5 equiv) was added, followed by diethyl azodicarboxylate (1.64 equiv) dropwise, at 0 °C. The mixture was allowed to warm to room temperature for 2.5 h. Solvents were evaporated in vacuo, and the crude was purified by silica gel flash chromatography (petroleum ether/ethyl acetate gradient) to obtain the desired compound (296 mg, 1.02 mmol, 62% yield) as an oil. Compound **2h** was obtained in two steps with 37% overall yield from Cbz-L-Asp(OtBu)-OH. R_f petroleum ether/EtOAc (6/4, v/v): 0.90. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.26 (m, 5H, CHAr), 5.16−5.09 (m, 2H, CH_2Ph), 2.79 (ddd, J = 12.6, 6.0, 3.7 Hz, 1H, CHAz), 2.60 (dd, J = 16.1, 5.9 Hz, 1H, $CHCH_2C(O)$), 2.42 (d, J = 6.1 Hz,

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1H, CH_2, Az), 2.28 (dd, J = 16.1, 6.7 Hz, 1H, $CHCH_2C(O)$), 2.07 (d, J = 3.7 Hz, 1H, CH_2, Az), 1.44 (s, 9H, $3CH_3$, Boc). Data in accordance with the literature.[53]

(S)-4-Benzyloxazolidin-2-one (4). The protocol is adapted from the work of Cardillo et al.[34] The compound **2b** (160 mg, 0.68 mmol, 1 equiv) was dissolved in anhydrous toluene (35.7 mL/mmol), at room temperature under argon atmosphere, in a microwave tube. $BF_3{\cdot}Et_2O$ (1 equiv) was added, and then the tube was sealed and placed under microwave radiations (55 °C for 10 min, 100 W, and 1000 rpm). The reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate, and the organic layers were combined, dried on $MgSO_4$, filtered, and concentrated in vacuo, and the crude was purified by silica gel flash chromatography (dichloromethane/MeOH gradient) to afford the title compound (88 mg, 0.49 mmol, 73% yield) as a white solid. R_f dichloromethane/MeOH (95/5, v/v): 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.13 (m, 5H, CHAr), 5.38 (d, J = 4.0 Hz, 1H, NH), 4.87 (dq, J = 8.0, 6.7 Hz, 1H, CH), 3.58 (t, J = 8.4 Hz, 1H, OCH_2), 3.34 (dd, J = 8.5, 6.9 Hz, 1H, OCH_2), 3.15 (dd, J = 14.0, 6.2 Hz, 1H, CH_2Ph), 2.95 (dd, J = 14.0, 6.8 Hz, 1H, CH_2Ph). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.7 (s, C(O)), 135.3 (s, CAr), 129.5 (s, CHAr), 128.9 (s, CHAr), 127.3 (s, CHAr), 77.2 (s, CH), 45.1 (s, OCH_2), 40.7 (s, CH_2Ph). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{12}NO_2$ 178.0868, found 178.0868.

Benzyl (S)-(2-Hydroxy-1-phenylethyl)carbamate (1a). The title compound (3.76 g, 13.87 mmol, 95% yield) was obtained as a white powder following the procedure described by Sultane et al.[54] from commercially available L-phenylglycinol (2.00 g, 14.58 mmol). R_f petroleum ether/EtOAc (6/4, v/v): 0.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.23 (m, 10H, CH_{Ar}), 5.47 (s, 1H, NH), 5.11 (q, J = 12.2 Hz, 2H, OCH_2Ph), 4.86 (s, 1H, CH), 3.95−3.80 (m, 2H, CH_2OH). Data in accordance with the literature.[54]

Benzyl (S)-(1-Hydroxy-3-(1H-indol-3-yl)propan-2-yl)carbamate (1d). The title compound (720 mg, 2.22 mmol, 42% yield) was obtained as a white foam following the procedure from Yeung et al.[55] from the commercially available L-tryptophanol (1.00 g, 5.26 mmol). R_f petroleum ether/EtOAc (6/4, v/v): 0.10. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H, NH), 7.65 (d, J = 7.5 Hz, 1H, CHAr), 7.43−7.28 (m, 6H), 7.21 (t, J = 7.5 Hz, 1H, CHAr), 7.15−7.07 (m, 1H, CHAr), 7.03 (s, 1H, CHAr), 5.10 (s, 2H, CH_2Ph), 5.04 (br s, 1H, NH), 4.16−3.95 (m, 1H, CH), 3.68 (ddd, J = 15.4, 9.7, 4.2 Hz, 2H, CCH_2CH), 3.03 (d, J = 6.8 Hz, 2H, CH_2OH). Data in accordance with the literature.[55,56]

tert-Butyl (S)-(1-(4-(Benzyloxy)phenyl)-3-hydroxypropan-2-yl)-carbamate (1e). The protocol was adapted from Jung et al.[30] Boc-Tyr(OBn)-OH (1.00 g, 2.69 mmol, 1 equiv) was dissolved in anhydrous THF (2.3 mL/mmol) at 0 °C under argon atmosphere. $BH_3{\cdot}THF$ (1 M in THF, 2.5 equiv) was added dropwise over 20 min (exothermic reaction) to the solution, and the reaction mixture was stirred for 1 h at 0 °C and then 3 h at room temperature. Methanol was slowly added at 0 °C to quench the reaction. Volatiles were removed in vacuo, and the crude was dissolved in methanol and then concentrated several times. The crude was purified by flash chromatography on silica gel (dichloromethane/MeOH gradient) to obtain the title product as a white solid (958 mg, 2.68 mmol, 99% yield). R_f dichloromethane/MeOH (95/5, v/v): 0.55. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.29 (m, 5H, CHAr), 7.12 (d, J = 8.5 Hz, 2H, CHAr), 6.92 (d, J = 8.5 Hz, 2H, CHAr), 5.05 (s, 2H, CCH_2Ph), 3.82 (m, 1H, CH), 3.60 (ddd, J = 43.3, 11.3, 5.4 Hz, 2H, $CHCH_2Ph$), 2.78 (d, J = 7.2 Hz, 2H, CH_2OH), 1.42 (s, 9H, $3CH_3$, Boc). Data in accordance with the literature.[30,57]

Benzyl tert-Butyl (6-hydroxyhexane-1,5-diyl)-(S)-dicarbamate (1i). The L-Nα-Z,Nε-BocLys-OH (2.00 g, 5.26 mmol, 1 equiv) was dissolved in anhydrous THF (11.0 mL/mmol) under argon atmosphere. *N*-Methylmorpholine and ethyl chloroformate (1 equiv) were added at −10 °C, and the reaction mixture was stirred for 30 min at −10 °C. $LiAlH_4$ (2 equiv) was then slowly added dropwise, and the reaction was allowed to warm at room temperature. The reaction mixture was stirred overnight at room temperature. The reaction was quenched by the slow addition of a 4.5% NaOH solution in water, at 0 °C. After being stirred for 1 h 30, the reaction mixture was filtered on a glass filter with dichloromethane. The filtrate was concentrated, dissolved in ethyl acetate, and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude was purified by silica gel flash chromatography (dichloromethane/MeOH gradient) to obtain the title compound as an oil (1.53 g, 4.18 mmol, 80% yield). R_f dichloromethane/MeOH (95/5, v/v): 0.40. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.28 (m, 5H, CHAr), 5.10 (s, 2H, CH_2Ph), 5.15−5.01 (m, 3H), 4.57 (s, 1H), 3.74−3.54 (m, 3H), 3.22−3.13 (m, 1H), 3.12−3.01 (m, 1H), 2.46 (br s, 1H, OH), 1.67−1.57 (m, 2H), 1.53−1.33 (m, 17H). Data in accordance with the literature.[58]

Di-tert-butyl (6-Hydroxyhexane-1,5-diyl)(S)-dicarbamate (1j). The L-Nα,Nε-bisBoc-Lys-OH dicyclohexylammonium (600 mg, 1.14 mmol, 1 equiv) was dissolved in anhydrous THF (11 mL/mmol) under argon atmosphere. *N*-Methylmorpholine and ethyl chloroformate (1 equiv) were added at −10 °C, and the reaction mixture was stirred for 30 min at −10 °C. $LiAlH_4$ (2.0 equiv) was then slowly added dropwise, and the reaction was allowed to warm at room temperature. The reaction mixture was stirred overnight and then quenched by the slow addition of a 4.5% NaOH solution in water, at 0 °C. After being stirred for 1 h 30, the reaction mixture was filtered on a glass filter. The filtrate was concentrated in vacuo, dissolved in ethyl acetate, and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (dichloromethane/MeOH gradient) to obtain the title compound as a colorless oil (300 mg, 0.90 mmol, 80% yield). R_f dichloromethane/MeOH (95/5, v/v): 0.25. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (br s, 1H, NH), 4.58 (br s, 1H, NH), 3.72−3.46 (m, 3H, CH_2, CH), 3.23−3.13 (m, 1H), 3.13−3.05 (m, 1H), 2.69−2.43 (m, 1H, OH), 1.63−1.54 (m, 2H, CH_2), 1.52−1.25 (m, 22H, $6CH_3$, Boc, $2CH_2$). Data in accordance with the literature.[59]

Benzyl ((1R,2R)-2-Hydroxycyclohexyl)carbamate (1k). The protocol was adapted from Luna et al.[60] The (1*R*,2*R*)-*trans*-2-aminocyclohexanol hydrochloride (2.00 g, 13.19 mmol, 1 equiv) was dissolved in distilled water (1.7 mL/mmol), and K_2CO_3 (1.2 equiv) was added. Then benzyl chloroformate (CbzCl, 1.2 equiv) was added dropwise at 0 °C. A white precipitate was formed. The reaction mixture was allowed to warm to room temperature and stirred overnight. Dichloromethane was added to the reaction mixture, and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried on $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified on silica gel (petroleum ether/ethyl acetate gradient) to afford the title compound (3.72 g, 13.00 mmol, 98% yield) as a white solid. R_f petroleum ether/EtOAc (7/3, v/v): 0.20. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.28 (m, 5H, CHAr), 5.20−5.04 (m, 2H, CH_2Ph), 4.72 (br s, 1H, NH), 3.40 (m, 1H, CH), 3.32 (m, 1H, CH), 2.80 (br s, 1H, OH), 2.11−1.93 (m, 2H, CH_2), 1.71 (m, 2H, CH_2), 1.40−1.09 (m, 4H). Data in accordance with the literature.[60]

Benzyl ((1R,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)-carbamate (1l). The (1*R*,2*R*)-(−)-1-amino-2-indanol (1.00 g, 6.70 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (1 mL/mmol) at 0 °C under argon atmosphere. Benzyl chloroformate (CbzCl, 1 equiv) was added at 0 °C, followed by pyridine (1.5 equiv), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of brine, and water was added to dissolve the salts. The mixture was extracted with dichloromethane, and the resulting emulsion was filtered on a hydrophobic filter cartridge. The prganic layers were recovered, dried on $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (petroleum ether/ethyl acetate gradient) to obtain the title compound (1.20 g, 4.24 mmol, 63% yield) as a white solid. R_f hexane/EtOAc (66/34, v/v): 0.30. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (dd, J = 4.2, 1.8 Hz, 2H, CHAr), 7.38−7.33 (m, 1H, CHAr), 7.29−7.17 (m, 6H, CHAr), 5.23 (s, 1H, NH), 5.19 (q, J = 12.2 Hz, 1H, OCH_2Ph), 4.99 (t, J = 6.1 Hz, 1H, CHNH), 4.46 (dd, J = 14.7, 7.4 Hz, 1H, CHOH), 3.31 (dd, J = 15.8, 7.7 Hz, 1H, CH_2), 2.93 (dd, J = 15.8, 8.1 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR (151 MHz,

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$CDCl_3$): δ 157.9 (s, C(O)Cbz), 140.3 (s, CAr), 139.1 (s, CAr), 136.1 (s, CAr), 128.7 (m, CHAr), 127.5 (s, CHAr), 125.4 (s, CHAr), 123.1 (s, CHAr), 82.2 (s, CHOH), 67.6 (s, OCH_2Ph), 64.6 (s, 1C, CHNH), 38.6 (s, CH_2). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}NO_3$ 284.1281, found 284.1285.

*tert-Butyl ((1R,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)-carbamate (**1m**).* The (1*R*,2*R*)-(−)-1-amino-2-indanol (1.00 g, 6.70 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (1.8 mL/mmol) at room temperature under argon atmosphere. Triethylamine (Et_3N, 1.5 equiv) was added, followed by Boc_2O (di-*tert*-butyl dicarbonate, 1.2 equiv). The reaction was stirred at room temperature for 6 h. The reaction was quenched by addition of an aqueous solution of saturated $NaHCO_3$ and extracted with dichloromethane. The emulsion was filtered on a hydrophobic filter cartridge. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to obtain the title compound (1.67 g, 6.7 mmol, quantitative yield) as a white solid. R_f hexane/EtOAc (66/34, v/v): 0.50. ^1H NMR (600 MHz, $CDCl_3$): δ 7.30−7.14 (m, 4H, CHAr), 5.06 (s, 1H, NH), 4.90 (t, *J* = 5.9 Hz, 1H, CHNH), 4.41 (dd, *J* = 14.2, 7.8 Hz, 1H, CHOH), 4.30 (s, 1H, OH), 3.28 (dd, *J* = 15.8, 7.7 Hz, 1H, CH_2), 2.91 (dd, *J* = 15.7, 8.1 Hz, 1H, CH_2), 1.50 (s, 9H, CH_3, Boc). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 157.6 (s, C(O)Boc), 140.3 (s, $CArCH_2$), 139.5 (s, CArCHNH), 128.6 (s, CH), 127.3 (s, CH), 125.3 (s, CH), 123.1 (s, CH), 82.2 (s, CHOH), 80.6 (s, $C(CH_3)_3$), 64.2 (s, CHNH), 38.5 (s, CH_2), 28.6 (s, CH_3, Boc). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{20}NO_3$ 250.1437, found 250.1434.

*Benzyl ((1S,2R)-2-Hydroxy-1,2-diphenylethyl)carbamate (**1n**).* The (1*R*,2*S*)-2-amino-1,2-diphenylethanol (2.00 g, 9.38 mmol, 1 equiv) was dissolved in anhydrous THF (2.77 mL/mmol) at 0 °C under argon atmosphere. Solid $NaHCO_3$ (2 equiv) was then added, followed by benzyl chloroformate (CbzCl, 1.2 equiv) dropwise. The mixture was stirred overnight at room temperature until completion of the reaction (TLC monitoring). The reaction was quenched by addition of water and extracted with ethyl acetate. The organic layers were acidified with HCl 1 N, washed with brine, dried on $MgSO_4$, filtrated, and concentrated in vacuum. The crude was purified by silica gel flash chromatography (dichloromethane/MeOH gradient) to obtain the title compound (3.25 g, 9.38 mmol, quantitative yield) as a white powder. R_f petroleum ether/EtOAc (7/3, v/v): 0.50. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.28 (m, 5H, CHAr), 7.24−7.19 (m, 6H, CHAr), 7.04 (m, 4H, CHAr), 5.59 (br s, 1H, NH), 5.15−4.99 (m, 4H, CHOH, CHNH, CH_2Ph), 2.39 (br s, 1H, OH). Data in accordance with the literature.[61]

General Procedure for the Preparation of *N*-Methylene-*gem*-bisphosphonate Aziridines from *N*-Carbamoylaziridines. Freshly distilled diethyl phosphite (6.1 equiv) was dissolved in anhydrous THF (0.5 mL/mmol of diethyl phosphite) under argon atmosphere and cooled to −78 °C. Then LiHMDS (1 M in THF, 6 equiv) was added, and the reaction mixture was stirred for 30 min at −78 °C. A solution of the *N*-carbamoylaziridine (1 equiv) in anhydrous THF (2.8 mL/mmol of aziridine) was added dropwise to the reaction, which was then allowed to warm to room temperature. The reaction mixture was stirred at temperature T^0 until completion of the reaction (TLC monitoring). The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl until dissolution of the salts formed. The mixture was extracted twice with ethyl acetate. The organic layers were dried on $MgSO_4$, filtered, and concentrated in vacuo, and the crude was purified by silica gel flash chromatography (dichloromethane/MeOH gradient) to afford the desired product.

*Tetraethyl ((2-Phenylaziridin-1-yl)methylene)-(S)-bis-(phosphonate) (**3a**).* The title compound (100 mg, 0.39 mmol, 45% yield) was obtained as a colorless oil following the procedure described above, after being stirred for 1 h at room temperature, from compound **2a** (73 mg, 0.18 mmol). R_f dichloromethane/MeOH (95/5, v/v): 0.30. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31−7.24 (m, 4H, CHAr), 7.21 (m, 1H, CHAr), 4.37−4.24 (m, 4H, $2CH_2CH_3$), 4.21−3.98 (m, 4H, $2CH_2CH_3$), 2.84 (ddd, *J* = 6.1, 4.1, 1.7 Hz, 1H, CHAz), 2.61 (t, *J* = 18.0 Hz, 1H, PCHP), 2.19 (d, *J* = 3.9 Hz, 1H, CH_2, Az), 2.14 (dd, *J* = 6.7, 1.8 Hz, 1H, CH_2, Az), 1.39 (td, *J* = 7.1, 4.1 Hz, 6H, $2CH_2CH_3$), 1.18 (dt, *J* = 14.2, 7.1 Hz, 6H, $2CH_2CH_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 139.3 (s, CAr), 128.2 (s, CHAr), 127.2 (s, CHAr), 126.5 (s, CHAr), 65.1 (t, *J* = 149.3 Hz, PCHP), 63.6 (d, *J* = 7.1 Hz, 2C, CH_2CH_3), 63.4−63.1 (m, 2C, CH_2CH_3), 43.6 (d, *J* = 15.6 Hz, CHAz), 40.2 (d, *J* = 15.9 Hz, CH_2, Az), 16.8−16.6 (m, 2C, $2CH_2CH_3$), 16.4 (d, *J* = 6.8 Hz, 2C, $2CH_2CH_3$). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 17.6 (d, J_{PP} = 2.6 Hz), 17.4 (d, J_{PP} = 2.6 Hz). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{30}NO_6P_2$ 406.1548, found 406.1549.

*Tetraethyl ((2-Benzylaziridin-1-yl)methylene)-(S)-bis-(phosphonate) (**3b**).* The title compound (264 mg, 0.63 mmol, 84% yield) was obtained as a colorless oil following the procedure described above (overnight stirring at room temperature) from compound **2c** (200 mg, 0.75 mmol) or from compound **2b** (stirring 2 h at 80 °C, 500 mg, 2.14 mmol) with 69% yield (630 mg, 1.50 mmol). R_f dichloromethane/MeOH (95/5, v/v): 0.35. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30−7.18 (m, 5H, CHAr), 4.32−4.18 (m, 8H, CH_2CH_3), 3.33 (dd, *J* = 14.1, 3.6 Hz, 1H, CH_2Ph), 2.40 (t, *J* = 18.1 Hz, 1H, PCHP), 2.40 (dd, *J* = 13.4, 9.4 Hz, 1H, CH_2Ph), 2.11−2.00 (m, 1H, CHAz), 1.93 (d, *J* = 3.9 Hz, 1H, CH_2, Az), 1.72 (d, *J* = 8.3 Hz, 1H, CH_2, Az), 1.38 (t, *J* = 7.1 Hz, 6H, CH_2CH_3), 1.35 (dt, *J* = 7.0, 4.4 Hz, 6H, CH_2CH_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 138.8 (s, CAr), 129.1 (s, 2C, CHAr), 128.5 (s, 2C, CHAr), 126.4 (s, CHAr), 64.9 (t, *J* = 150.1 Hz, PCHP), 63.3 (d, *J* = 10.6 Hz, 2C, CH_2CH_3), 63.1 (d, *J* = 6.9 Hz, 2C, CH_2CH_3), 43.1 (d, *J* = 16.2 Hz, CHAz), 38.9 (s, CH_2Ph), 36.5 (d, *J* = 17.0 Hz, CH_2 Az), 16.7 (d, *J* = 10.3 Hz, 2C, CH_2CH_3), 16.6 (d, *J* = 10.1 Hz, 2C, CH_2CH_3). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 18.0 (s, 1P), 17.9 (s, 1P). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{32}NO_6P_2$ 420.1705, found 420.1709.

*Tetraethyl ((2-((1H-indol-3-yl)methyl)aziridin-1-yl)methylene)-(S)-bis(phosphonate) (**3d**).* The title compound (53 mg, 0.11 mmol, 45% yield) was obtained as a colorless oil following the procedure described above (4h stirring at room temperature) from compound **2d** (78 mg, 0.25 mmol).

R_f dichloromethane/MeOH (95/5, v/v): 0.50. ^1H NMR (600 MHz, $CDCl_3$): δ 8.46 (s, 1H, NH), 7.60 (dd, *J* = 7.8, 0.7 Hz, 1H, CHAr), 7.36 (d, *J* = 8.1 Hz, 1H, CHAr), 7.19−7.11 (m, 1H, CHAr), 7.11−7.05 (m, 1H, CHAr), 7.02 (d, *J* = 2.0 Hz, 1H, NHCHArC), 4.35−4.17 (m, 8H, $4CH_2CH_3$), 3.50 (dd, *J* = 14.8, 3.3 Hz, 1H, $CHCH_2C$), 2.55−2.47 (m, 1H, $CHCH_2C$), 2.43 (t, *J* = 18.2 Hz, 1H, PCHP), 2.19−2.13 (m, 1H, CHAz), 1.96 (d, *J* = 4.0 Hz, 1H, CH_2, Az), 1.72 (d, *J* = 7.0 Hz, 1H, CH_2, Az), 1.39−1.36 (m, 6H, $2CH_2CH_3$), 1.37−1.33 (m, 6H, $2CH_2CH_3$). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 136.4 (s, CAr), 127.8 (s, CAr), 122.1 (s, CHAr), 121.9 (s, CHAr), 119.3 (s, CHAr), 119.1 (s, CHAr), 112.8 (s, CAr), 111.3 (s, CCHArNH), 65.1 (t, *J* = 150.3 Hz, PCHP), 63.4−62.7 (m, 4C, CH_2CH_3), 42.8 (d, *J* = 16.1 Hz, CHAz), 37.0 (d, *J* = 16.8 Hz, CH_2, Az), 28.6 (s, $CHCH_2C$), 16.6 (s, 4C, CH_2CH_3). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 18.1 (s, 2P). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{33}N_2O_6P_2$ 459.1814, found 459.1814.

*Tetraethyl ((2-(4-(benzyloxy)benzyl)aziridin-1-yl)methylene)(S)-bis(phosphonate) (**3e**).* The title compound (108 mg, 0.21 mmol, 46% yield) was obtained as a colorless oil following the procedure described above (3h stirring at 80 °C) from compound **2e** (150 mg, 0.44 mmol).

R_f dichloromethane/MeOH (95/5, v/v): 0.25. ^1H NMR (500 MHz, $CDCl_3$): δ 7.44−7.40 (m, 2H, CHAr), 7.40−7.35 (m, 2H, CHAr), 7.34−7.29 (m, 1H, CHAr), 7.14−7.09 (m, 2H, CHAr), 6.92−6.87 (m, 2H, CHAr), 5.03 (s, 2H, OCH_2Ph), 4.32−4.17 (m, 8H, $4CH_2CH_3$), 3.26 (dd, *J* = 14.2, 3.6 Hz, 1H, $CHCH_2Ph$), 2.39 (t, *J* = 18.1 Hz, 1H, PCHP), 2.34 (dd, *J* = 14.2, 8.6 Hz, 1H, $CHCH_2Ph$), 2.06−1.97 (m, 1H, CHAz), 1.90 (d, *J* = 4.0 Hz, 1H, CH_2, Az), 1.70 (dd, *J* = 6.4, 1.1 Hz, 1H, CH_2, Az), 1.37 (t, *J* = 7.1 Hz, 6H, $2CH_2CH_3$), 1.36−1.33 (m, 6H, $2CH_2CH_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 157.5 (s, OCAr), 137.3 (s, CAr), 131.1 (s, CAr), 130.0 (s, 2C, CHAr), 128.7 (s, 2C, CHAr), 128.0 (s, CHAr), 127.6 (s, 2C, CHAr), 115.0 (s, 2C, CHAr), 70.1 (s, OCH_2Ph), 64.91 (t, *J* = 150.0 Hz, 1C, PCHP), 63.5−62.9 (m, 4C, CH_2CH_3), 43.2 (d, *J* = 16.3 Hz, CHAz), 38.0 (s, $CHCH_2Ph$), 36.4 (d, *J* = 16.8 Hz, CH_2, Az), 16.6 (s, 4C, CH_2CH_3). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 18.0 (s,

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2P). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{38}NO_7P_2$ 526.2124, found 526.2131.

*(S)-Tetraethyl ((2-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)aziridin-1-yl)methylene)bis(phosphonate) (**3f**).* The title compound (133 mg, 0.28 mmol, 50% yield) was obtained as a colorless oil following the procedure described above (stirring for 7h at 55 °C) from compound **2f** (162 mg, 0.56 mmol). R_f dichloromethane/MeOH (95/5, v/v): 0.25. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H, NCHArN), 7.80 (dd, J = 5.9, 3.0 Hz, 1H, HAr), 7.41 (dd, J = 5.9, 2.9 Hz, 1H, HAr), 7.31−7.26 (m, 2H, HAr), 4.51−4.34 (m, 2H, CH_2N), 4.31−4.15 (m, 8H, 4 CH_2CH_3), 2.34 (t, J = 18.1 Hz, 1H, PCHP), 2.19−1.95 (m, 1H, CH_2CH_2N), 1.92−1.86 (m, 1H, CH), 1.70 (dd, J = 9.6, 5.2 Hz, 2H, $CHCH_2$N), 1.35 (t, J = 7.1 Hz, 12H, 4 CH_3CH_2). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 144.0 (s, CAr), 143.3 (s, C-2), 133.8 (s, CAr), 122.9 (s, CAr), 122.2 (s, CAr), 120.6 (s, CAr), 109.8 (s, CAr), 64.9 (t, J = 150.5 Hz, PCHP), 63.4 (dd, J = 26.4, 6.4 Hz, 4C, CH_2CH_3), 42.8 (s, CH_2CH_2N), 39.3 (d, J = 20.5 Hz, CHN), 35.9 (d, J = 15.0 Hz, $CHCH_2$N), 33.4 (d, J = 40.2 Hz, CH_2CH_2N), 16.7 (s, 4C, CH_3CH_2). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.8 (s, 1P), 17.7 (s, 1P). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{34}N_3O_6P_2$ 474.1923, found 474.1932.

*Tetraethyl (((S)-2-((S)-sec-Butyl)aziridin-1-yl)methylene)bis(phosphonate) (**3g**).* The title compound (121 mg, 0.31 mmol, 41% yield) was obtained as a colorless oil following the procedure described above (stirring for 2 h at 80 °C) from compound **2g** (150 mg, 0.75 mmol). R_f petroleum ether/EtOAc (7/3, v/v): 0.10. ^{1}H NMR (500 MHz, MeOD): δ 4.31−4.15 (m, 8H, 4CH_2CH_3), 2.71 (t, J = 18.8 Hz, 1H, PCHP), 1.87 (tdd, J = 6.3, 4.5, 1.7 Hz, 1H, CHAz), 1.84−1.81 (m, 1H, CH_2, Az), 1.76−1.67 (m, 1H, $CHCH_2CH_3$), 1.66 (dd, J = 6.5, 1.3 Hz, 1H, CH_2, Az), 1.44−1.39 (m, 1H, $CHCH_3$), 1.37 (tdd, J = 7.1, 2.5, 1.2 Hz, 12H, 4 CH_2CH_3), 1.31−1.19 (m, 1H, $CHCH_2CH_3$), 0.94 (t, J = 7.5 Hz, 3H, CH_3CH_2CH), 0.81 (d, J = 6.9 Hz, 3H, CH_3CH). ^{13}C{^{1}H} NMR (126 MHz, MeOD): δ 65.0 (t, J = 152.0 Hz, PCHP), 64.6 (ddd, J = 17.5, 13.8, 6.8 Hz, 4C, CH_2CH_3), 47.7 (dd, J = 13.7, 5.2 Hz, CHAz), 37.9 (s, $CHCH_3$), 35.3 (d, J = 14.6 Hz, CH_2 Az), 28.6 (s, $CHCH_2CH_3$), 16.8 (dd, J = 10.8, 4.8 Hz, 4C, CH_2CH_3), 14.9 (s, $CHCH_3$), 11.9 (s, $CHCH_2CHy$). ^{31}P{^{1}H} NMR (202 MHz, MeOD): δ 18.2 (d, J_{PP} = 5.1 Hz), 18.1 (d, J_{PP} = 5.1 Hz). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{34}NO_6P_2$ 386.1861, found 386.1860.

*tert-Butyl (S)-2-(1-(Bis(diethoxyphosphoryl)methyl)aziridin-2-yl)acetate (**3h**).* The title compound (30 mg, 0.07 mmol, 20% yield) was obtained as a colorless oil following the procedure described above (stirring for 2 h at room temperature) from compound **2h** (100 mg, 0.34 mmol). R_f dichloromethane/MeOH 95/5 (v/v): 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.30−4.16 (m, 8H, 4CH_2CH_3), 3.01 (dd, J = 15.9, 3.1 Hz, 1H, $CH_2C(O)$), 2.38 (t, J = 18.1 Hz, 1H, PCHP), 2.11−2.04 (m, 1H, CHAz), 1.98 (dd, J = 15.9, 9.3 Hz, 1H, $CH_2C(O)$), 1.95 (d, J = 3.8 Hz, 1H, CH_2, Az), 1.81 (d, J = 6.5 Hz, 1H, CH_2, Az), 1.43 (s, 9H, 3CH_3, tBu), 1.39−1.31 (m, 12H, 4CH_2CH_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.8 (s, C(O)tBu), 80.8 (s, $C(CH_3)_3$, tBu), 66.0−63.5 (t, J = 150.3 Hz, PCHP), 63.4−63.0 (m, 4C, 4CH_2CH_3), 39.0 (s, $CH_2C(O)$), 38.4 (d, J = 15.6 Hz, CHAz), 36.2 (d, J = 15.3 Hz, 2C, CH_2, Az), 28.2 (s, 3C, 3CH_3, tBu), 16.6 (s, 4C, 4CH_2CH_3). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.8 (d, J_{PP} = 3.3 Hz, 1P), 17.7 (d, J_{PP} = 3.3 Hz, 1P). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{36}NO_8P_2$ 444.1911, found 444.1913.

*tert-Butyl (S)-(4-(1-(Bis(diethoxyphosphoryl)methyl)aziridin-2-yl)butyl)carbamate (**3i**).* The title compound (115 mg, 0.23 mmol, 40% yield) was obtained as colorless oil following the procedure described above (stirring for 4 h at room temperature) from compound **2i** (200 mg, 0.58 mmol). R_f dichloromethane/MeOH (95/5, v/v): 0.26. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.71 (s, 1H, NH), 4.31−4.16 (m, 8H, 4CH_2CH_3), 3.15−3.06 (m, 2H, $NHCH_2$), 2.34 (t, J = 18.2 Hz, 1H, PCHP), 1.83−1.79 (m, 1H, CHAz), 1.79 (d, J = 4.3 Hz, 1H, CH_2, Az), 1.66 (d, J = 6.4 Hz, 1H, CH_2, Az), 1.56−1.43 (m, 6H, 3CH_2), 1.43 (s, 9H, CH_3, Boc), 1.39−1.34 (m, 12H, 4CH_2CH_3). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 156.2 (s, C(O)Boc), 65.3 (t, J = 150.3 Hz, PCHP), 63.3−62.8 (m, 4C, CH_2CH_3), 42.0 (d, J = 15.3 Hz, CHAz), 40.7 (s, CH_2NH), 36.7 (d, J = 16.3 Hz, CH_2, Az), 29.9 (s, 3C, 3CH_2), 28.6 (s, 3C, CH_3, Boc), 18.0−15.6 (m, 4C, CH_2CH_3). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 18 (d, J_{PP} = 3.2 Hz), 17.9 (d, J_{PP} = 3.2 Hz). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{43}N_2O_8P_2$ 501.2495, found 501.2497.

*Tetraethyl (((1R,6S)-7-Azabicyclo[4.1.0]heptan-7-yl)methylene)bis(phosphonate) (**3k**).* The title compound (120 mg, 0.31 mmol, 72% yield) was obtained as a colorless oil following the procedure described above (stirring for 2 h at room temperature) from compound **2k** (100 mg, 0.43 mmol). R_f dichloromethane/MeOH 95/5 (v/v): 0.25. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.32−4.16 (m, 8H, 4CH_2CH_3), 2.39 (t, J = 18.0 Hz, 1H, PCHP), 1.94−1.87 (m, 4H, 2CH_2, 2CHAz), 1.77−1.70 (m, 2H, CH_2), 1.35 (td, J = 7.1, 5.9 Hz, 12H, 4CH_2CH_3), 1.34−1.30 (m, 2H, 2CH_2), 1.20−1.11 (m, 2H, 2CH_2). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 64.7 (t, J = 149.8 Hz, PCHP), 63.5−62.4 (m, 4C, 4CH_2CH_3), 41.3 (d, J = 16.4 Hz, 2C, 2CHAz), 24.1 (s, 2C, 2CH_2), 20.5 (s, 2C, 2CH_2), 17.0−16.3 (m, 4C, 4CH_2CH_3). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 18.2 (s, 2P). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{32}NO_6P_2$ 384.1705, found 384.1705.

*(1aR,6aS)-1,1a,6,6a-Tetrahydroindeno[1,2-b]azirine (**3l**).* The title compound (57.7 mg, 0.44 mmol, 97% yield) was obtained as a solid following the procedure described above (overnight stirring at room temperature) starting from compound **2l** (*N*-Cbz, 120 mg, 0.45 mmol) or from compound **3m** (*N*-Boc, 120 mg, 0.52 mmol)) with 84% yield (57 mg, 0.43 mmol). R_f dichloromethane/MeOH (95/5, v/v): 0.50. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50−7.45 (m, 1H, CHAr), 7.36−7.24 (m, 2H, CHAr), 7.22 (d, J = 7.5 Hz, 1H, CHAr), 6.84 (s, 1H, NH), 5.93 (d, J = 7.5 Hz, 1H, CH), 4.64 (t, J = 7.0 Hz, 1H, CH), 3.21 (dd, J = 17.1, 6.5 Hz, 1H, CH_2), 3.03 (d, J = 17.0 Hz, 1H, CH_2). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 140.9 (s, CAr), 138.4 (s, CAr), 130.3 (s, CHAr), 127.8 (s, CHAr), 126.3 (s, CHAr), 125.7 (s, CHAr), 84.4 (s, CHCH), 55.3 (s, CHCH), 39.6 (s, CH_2). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_9H_{10}N$ 132.0813, found 132.0814.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02434.

Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra of all new compounds described in the Experimental Section; copies of ^{1}H NMR spectra for known compounds or intermediates (PDF)

NMR comparative study for compounds **2d**/**3d** and **2g**/**3g** (PDF)

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