



Synthesis of N-methylene phosphonate aziridines: Reaction scope and mechanistic insights

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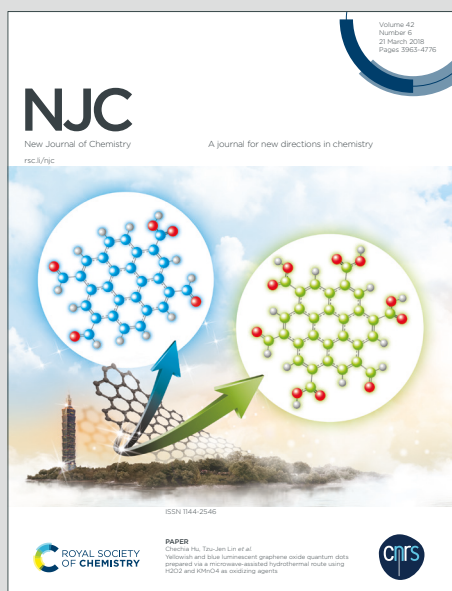
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Synthesis of *N*-methylene phosphonate aziridines: Reaction scope and mechanistic insightsThomas Cheviet,^a Ilyana Gonzales^a and Suzanne Peyrottes^{a*}Received 00th January 20xx,
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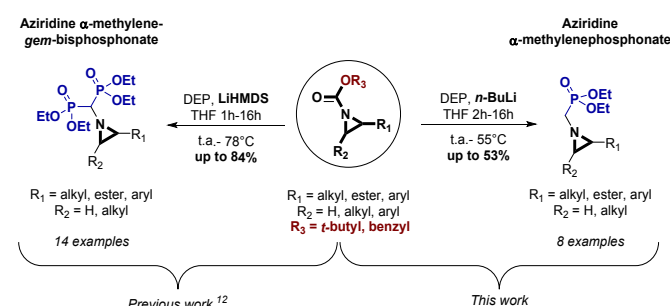
A series of *N*-carbamoyl aziridines has been treated by diethyl phosphite in presence of *n*-BuLi to afford α -methylene phosphonate aziridines in modest yields. The study of the reaction's scopes and the analysis of byproducts indicated that this transformation proceeds via a unique mechanism. The mechanism that produces the α -methylene phosphonate relies in the use of BuLi, where both the lithium ion and then the presence of the nucleophilic butyl is essential. In addition, the nature of the final compound, either α -methylene phosphonate or α -methylene-*gem*-bisphosphonate derivatives containing an aziridine motif, is highly dependent on the nature of the base used.

Introduction

For several decades, the synthesis and the study of the reactivity of three-membered ring heterocycles, especially oxiranes and aziridines, has attracted great attention.^{1–3} This is mainly associated with the ring-strain of these small-ring heterocycles, that makes them versatile intermediates in organic synthesis. Notably, aziridines are widely used as key building-blocks for the synthesis of aza-compounds (amino acids, modified sugars, natural products) and represent a valuable source of chiral centres due to their ability to endow regio- and stereoselective modifications.^{4–7} Except for aziridine-2-phosphonates that lead to α - or β -aminophosphonates as analogues of amino-acids,^{8, 9} the combination of chiral aziridines and phosphonate groups (widely used in medicinal chemistry as bio-isosteres of organic phosphates and insensitive to enzymatic cleavage) has been less explored. To our knowledge, only two articles described in the literature α -methylene phosphonate aziridines, as potential antiviral acyclonucleoside phosphonates,¹⁰ and they were obtained from the intramolecular cyclization of γ -halogenated- α -amino-phosphonates.¹¹

In a previous study, we proposed an original synthetic route involving lithiated diethylphosphite and *N*-carbamoyl aziridines as starting materials (Scheme 1) for the preparation of α -methylene-*gem*-bisphosphonate aziridines.¹² By replacing LiHMDS with *n*-BuLi, we observed the formation of a different final product identified as an α -methylene phosphonate aziridine. To investigate the scope of the reaction, a set of 13 *N*-

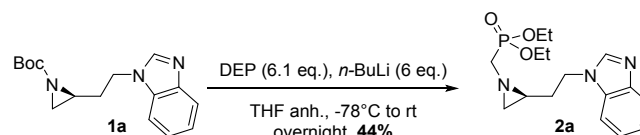
carbamoyl aziridines was used.¹² In addition, complementary experiments, isolation and identification of by-products supported the proposed mechanism leading to the formation of α -methylene phosphonate aziridines.



Scheme 1. The two series of compounds that may be obtained from *N*-carbamoyl aziridines.

Results and discussion

We initially observed the opportunistic formation of an α -methylene phosphonate aziridine from *N*-carbamoyl aziridine **1a** when using *n*-BuLi instead of LiHMDS to deprotonate the diethyl phosphite (Scheme 2).



Scheme 2. Initial observation of the formation of an α -methylene phosphonate aziridine from *N*-carbamoyl aziridine **1a**.

The identity of the resulting compound (**2a**) has been proposed on the basis of NMR and HRMS analysis. A single signal at 23 ppm was observed in ³¹P{¹H} NMR. The methylene group attached to the phosphorus atom produced two different

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signals in ^1H NMR (different multiplicity and δ values) due to the non-equivalence of the two protons (Figure 1A). The latter are coupling with the phosphorus atom and with their geminal neighbor with similar coupling constants ($\sim 12\text{--}20\text{ Hz}$, Figure 1B).

In addition, their signals correlate in HSQC $^1\text{H}\text{--}^{13}\text{C}$ with one carbon atom (Figure 1C), presenting a high coupling constant ($\sim 160\text{ Hz}$) due to the presence of the phosphorus atom.

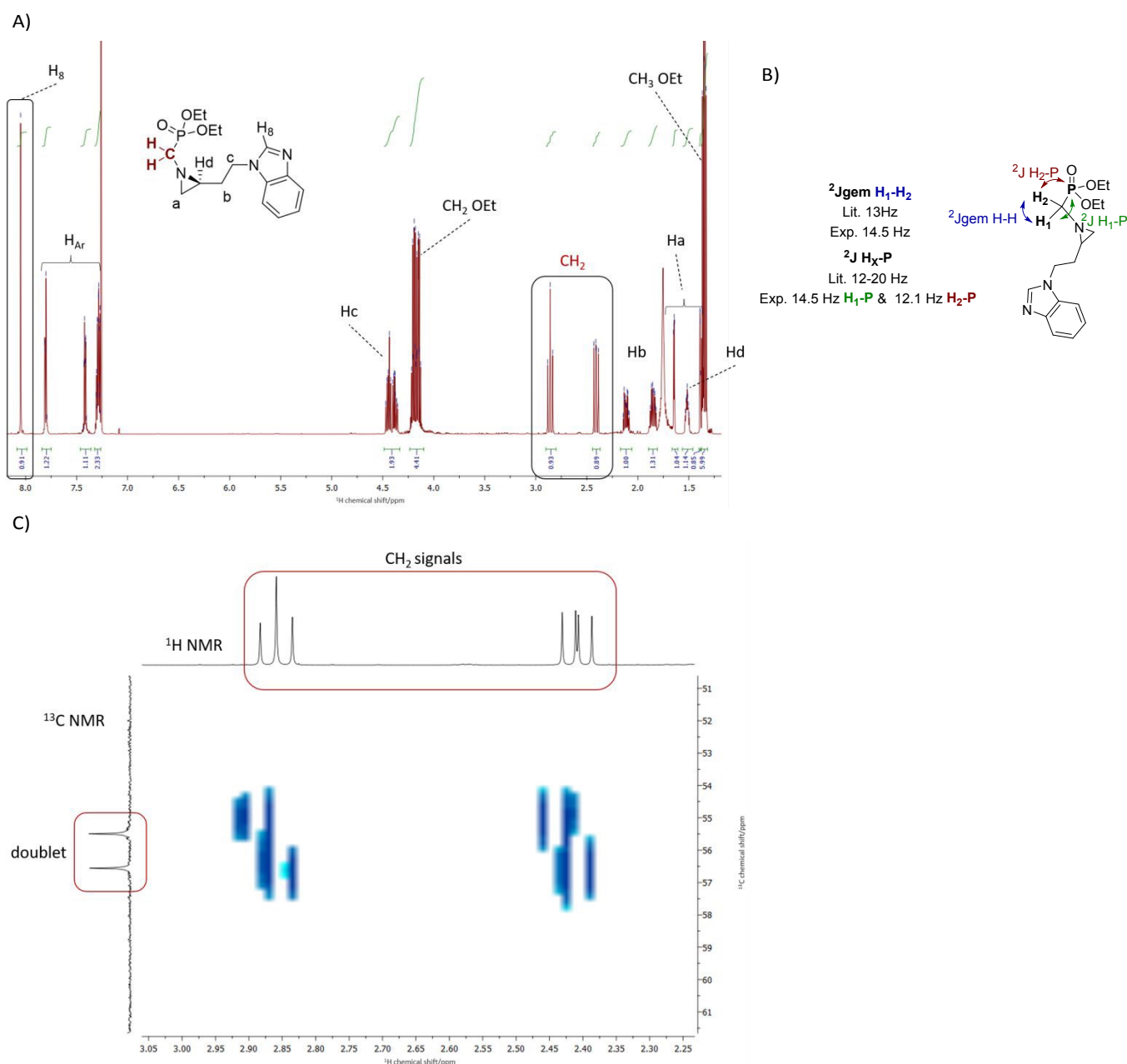


Figure 1. NMR Studies for structural identification of compound **2a**. A) ^1H NMR spectra and attribution; B) Coupling constants and relationship observed for the two protons of the *N*-methylene phosphonate motif; C) Detail of the HSQC $^1\text{H}\text{--}^{13}\text{C}$ NMR spectra

The scope of the reaction was examined by using *N*-carbamoyl aziridines previously prepared (**1a-d**, **1f-h**, **1j-m**)¹² or newly obtained (**1e** and **1i**). The following conditions were applied: 6.1 equivalents of diethylphosphite were treated by 6 equivalents of *n*-BuLi (2.5 M in THF) at -78°C , and the mixture was added to 1 equivalent of the aziridine substrate, then the reaction

mixture was heated at the indicated temperature until completion of the reaction (Table 1).

Impacts of the temperature, the nature of the carbamoyl protecting group (Boc versus Cbz), the nature of the phosphite and the presence of the aziridine ring were studied. Slightly better yields were obtained when the reaction was performed at 55°C (**2a**, **2b** from **1b**, **2f** and **2l**), and a *tert*-butoxycarbonyl

group was used (**2b** from **1b** and **1c**, **2d** from **1d** and **1e**, **2h** from **1h** and **1i**). The use of dibenzyl- or diisopropyl-phosphite instead of diethylphosphite did not lead to the formation of the expected derivatives (on the basis of **1b** as starting material) and very complex reaction mixtures were recovered instead. ³¹P NMR analysis of the crude material indicated only traces of the expected α-methylene phosphonate aziridine (data not shown). In addition, when the optimized conditions were applied on Cbz-L-phenylalaninol, no traces of the desired compound was observed, thus highlighting that the presence of the aziridine motif is mandatory.

As illustrated in Table 1, 10 out of the 13 starting materials were converted into the expected α-methylene phosphonate aziridines in low to modest yields. Numerous degradation/secondary products were observed and were difficult to resolve by silica gel chromatography, thus impacting yields. For aziridine **1g**, ³¹P NMR analysis of the reaction mixture

only revealed traces of the desired compound despite consumption of the starting material and this was not improved by the modification of the temperature (from rt to 55°C). This may be associated with the electronic and steric effects of the phenyl ring that led to the formation of a complex set of side-products.

One should note that for aziridines **1k** and **1l**, the formation of the α-methylene phosphonate aziridine was not observed when the reaction was carried out at room temperature (rt), and instead the corresponding α-methylene-gem-bisphosphonate derivatives were isolated in low yield (<25%), indicating that DEP/*n*-BuLi conditions may involve a reaction mechanism similar to the one proposed when using DEP/LiHMDS.¹² As previously observed,¹² no reaction occurred with compound **1m**, because of the highly constrained aziridine-ring, and the reduced product **2m** was exclusively isolated in high yield.

Table 1. Substrate scope for the formation of α-methylene phosphonate aziridines

$\text{R}_1\text{---N---R}_2$ (1) $\xrightarrow[\text{THF anh., 30 min at } -78^\circ\text{C, then T during t}]{\text{DEP (6.1 eq.)}, \text{ } n\text{-BuLi (6 eq.)}}$ $(\text{EtO})_2\text{P(=O)---N---R}_2$ (2)

2a
R=Boc, **1a**
rt, o.n., 44%^a
55°C, o.n., 54%^a

2b
R=Boc, **1b**
rt, o.n., traces^c
55°C, 2h, 51%^a

R=Cbz, **1c**
rt, 5h, 45%^a
55°C, 2h, 43%^a

2d
R=Boc, **1d**
55°C, 4h, 52%^a

R=Cbz, **1e**
55°C, 4h, 38%^a

2f
R=Cbz, **1f**
rt, 3h, <10%^b
55°C, 2h, 28%^b

2g
R=Cbz, **1g**
rt, 3h, traces^c
55°C, 4h, traces^c

2h
R=Boc, **1h**
55°C, 2h, 53%^a

R=Cbz, **1i**
55°C, 4h, 25%^a

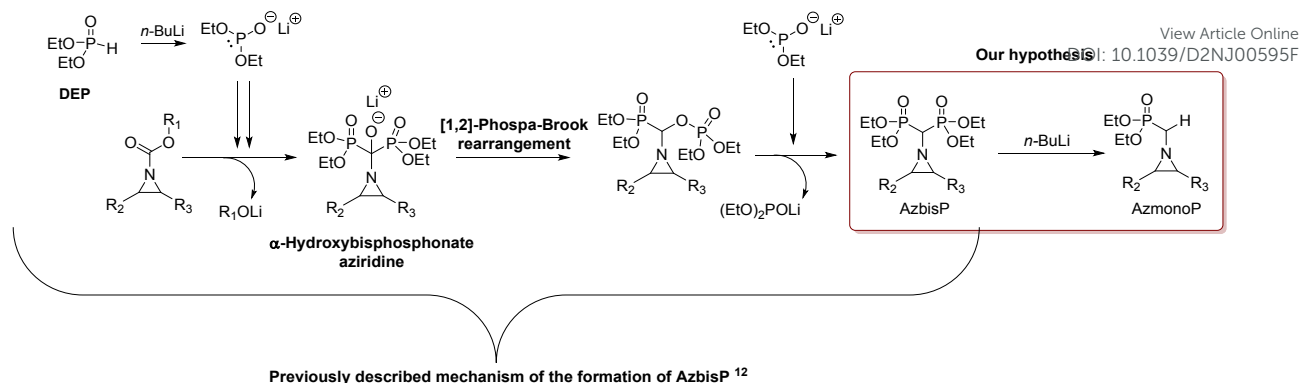
2j
R=Cbz, **1j**
55°C, 4h, 45%^a

2k
R=Cbz, **1k**
rt, 4h, 0%^a

2l
R=Cbz, **1l**
rt, 2h, 0%^a
55°C, 4h, 47%^a

2m
R=Boc, **1m**
55°C, 6h, 84%^a

[a] Isolated yield after purification by column chromatography. [b] Yields calculated from ¹H NMR spectra. [c] Observed by ³¹P NMR analysis of the crude mixture. rt means room temperature, o.n. means overnight reaction.



Scheme 3. Initial hypothesis for the formation of α-methylene phosphonate aziridine (AzmonoP) from the corresponding α-methylene-gem-bisphosphonate (AzbisP) derivative, and main steps of the previously described mechanism of formation of the latter.¹²

Mechanistic investigations

At first, the structural analogy between α-methylene phosphonate aziridine and α-methylene-gem-bisphosphonate derivatives, as well as the isolation of the latter in a few cases in DEP/*n*-BuLi conditions, led us to hypothesize a mechanism comparable to the one previously proposed (Scheme 3).¹² Briefly, the nucleophilic attack of the diethylphosphite anion onto the carbonyl group affords a putative α-hydroxy-bisphosphonate intermediate, that undergoes a [1,2]-Phospha-Brook rearrangement to form a phosphate moiety, which is then substituted by DEP to afford the bis-phosphonylated aziridine (the chelation of lithium ion is mandatory for each step to occur). Furthermore, the presence of α-methylene-gem-bisphosphonate aziridine as side-product in several reaction mixtures (DEP/*n*-BuLi conditions) suggested that it may serve as intermediate in the formation of the monophosphonylated compounds (Scheme 3). The conversion of α-methylene-gem-bisphosphonate to α-methylene-phosphonate derivative may be explained by the significant difference of the nucleophilic character of LiHMDS and *n*-BuLi. To confirm this assumption, the behavior of the tetraethyl ((2-benzylaziridin-1-yl)methylene)(S)-bis(phosphonate) **3** treated with a stoichiometric amount of DEP and *n*-BuLi was followed by ³¹P NMR analysis. After 3h (Figure 2), the presence of compound **2b** was observed, thus agreeing with our hypothesis. By-products **4**, **5**, and **6** were observed as well.

During the purification of **2b**, **2h** and **2l** we had the opportunity to isolate and identify by-products **4**, **5** and **6** (Scheme 4 & Figure S1). As we previously stated, the peculiarity of *n*-BuLi is that it can act both as a strong base (pK_a ~50) and a good nucleophile, in comparison to the previously used bases¹² (LiHMDS, NaHMDS, NaH or *t*BuOK, which are either non-nucleophilic or poorly nucleophilic), and is supposed to assist this step, because none of the other ones allowed the formation of α-methylene phosphonate aziridines. Formation of dibutyl phosphine oxide (**4**) may arise from the addition of the butyl anion on the diethylphosphite, leading to the elimination of the ethanoate

chains and supports the need to use excess of both reagents. Following the same line of thought, the two other products (**5** and **6**) may result from subsequent nucleophilic attack of the butyl anion on a phosphonylated intermediate (Scheme 4).

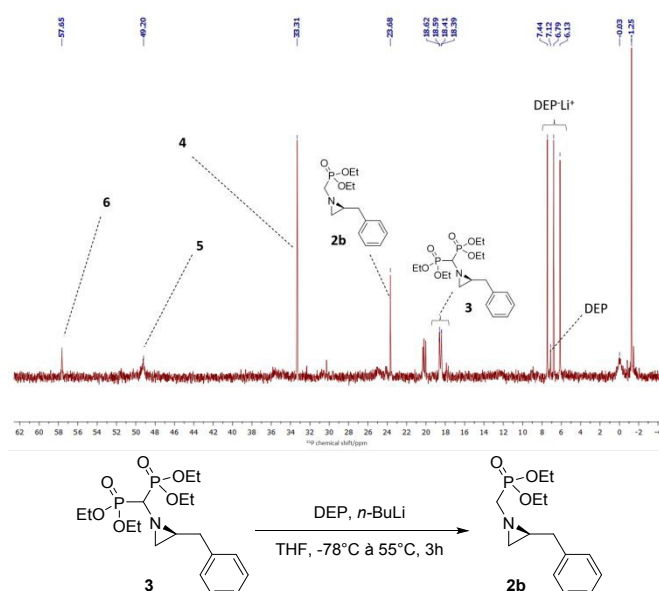
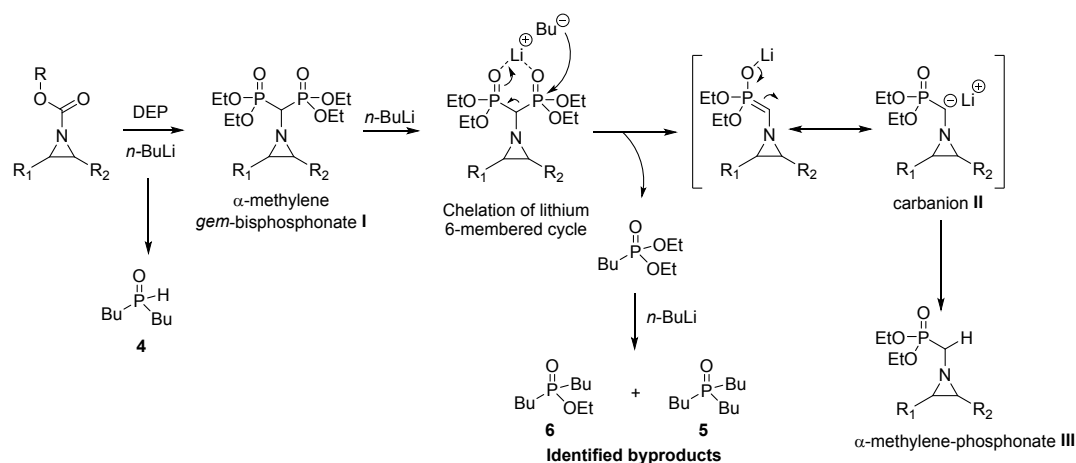


Figure 2. ³¹P NMR spectrum of the reaction mixture of **3** in presence of DEP/*n*-BuLi after 3h at 55°C.

Consequently, we proposed the mechanism presented in Scheme 4 and based on the elimination of one of the two diethyl phosphonate moieties from the α-methylene-gem-bisphosphonate (**I**) in presence of *n*-BuLi (with concomitant formation of by-products **5** and **6**), and leading to the formation of the carbanion **II**, that is quickly hydrolyzed to the expected α-methylene phosphonate aziridine. A similar elimination was previously proposed during the methanolysis of an α-amino bisphosphonate scaffold.¹³

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Scheme 4. Proposed mechanism for the formation of α-methylene phosphonate aziridine from the corresponding α-methylene-gem-bisphosphonate in presence of *n*-BuLi.

Experimental section

Materials and methods

NMR spectra were recorded in the Laboratoire de Mesures Physiques (LMP - University of Montpellier), on Brüker Avance spectrometers (400, 500 or 600 MHz for ^1H NMR; 101 or 126 MHz for ^{13}C NMR, and 162 or 202 MHz for ^{31}P NMR), at 20°C. Chemical shifts were reported in ppm (parts per million), and determined according to the residual solvent peak used as internal reference and relative to the trimethylsilyl peak (TMS) for ^1H and ^{13}C NMR, and according to an external reference (H_3PO_4) for ^{31}P NMR. When needed COSY (^1H 2D), HSQC ^1H - ^{13}C , and HMBC ^1H - ^{13}C were obtained to interpret and confirm ^1H and ^{13}C NMR spectra. Coupling values are indicated in Hertz (Hz). Signal multiplicities were reported as follows: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doubled doublet). Reaction monitoring using ^{31}P NMR were acquired in CDCl_3 (previously filtered on neutral aluminum oxide Al_2O_3), using oven-dried tubes (50°C) and flushed with argon before use. High resolution mass spectra (HRMS) were obtained from LMP, by ESI ionization (electrospray) in negative or positive mode, on a Q-TOF Synapt-G2-S spectrometer. 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 spraying with Hanes molybdate reagent or charring into a ninhydrin solution in ethanol. Flash chromatography on silica gel were performed on the automated system Biotage® IsoleraTM 4.

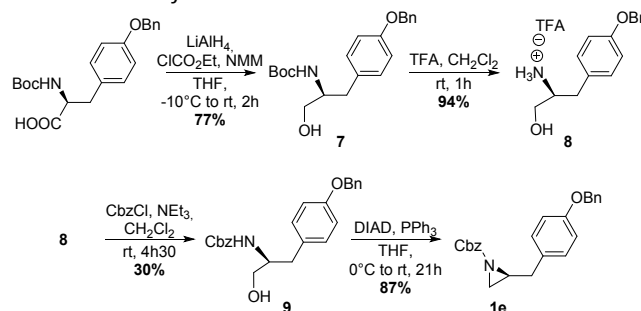
Reagents were from the following suppliers: Sigma-Aldrich, Alfa Aesar, Acros or TCI. Anhydrous solvents (stored on molecular sieves in sealed flasks) were from Sigma-Aldrich. Diethylphosphite (Acros) was distilled from KOH under reduced pressure and stored in a sealed round-bottom flask under argon atmosphere and in the dark.

Synthetic procedures

Synthesis and characterization of *N*-protected aziridines

N-carbamoyl aziridines **1a-d**, **1f-h** and **1j-m** were obtained according to our previously reported procedures.¹²

Benzyl (S)-2-(4-(benzyloxy)benzyl)aziridine-1-carbamate (1e) was obtained as follow:



tert-Butyl (*S*)-((1-(4-(benzyloxy)phenyl)-3-hydroxypropan-2-yl) carbamate (**7**)

The Boc-L-Tyr(Obn)-OH (1.0 g, 2.43 mmol, 1 eq.) was dissolved in anhydrous THF (2.30 mL/mmol) under argon atmosphere. *N*-Methyl morpholine (1 eq.) and ethyl chloroformate (1 eq.) were added at -10 °C, and the reaction mixture was stirred for 30 min

at -10°C . LiAlH_4 (1M in THF, 2.01 eq.) was then slowly added dropwise, and the reaction was allowed to warm at room temperature. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by the slow addition of an aqueous solution of KHSO_4 (1M) at 0°C . After being stirred for 15 min, the reaction mixture was filtered on a glass filter. The filtrate was concentrated, dissolved in ethyl acetate, and washed with saturated NaCl solution. The organic layer was dried over MgSO_4 , filtered, and concentrated *in vacuo*. The resulting crude was purified by silica gel flash chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$) to afford the title compound as a white solid (0.84 g, 2.34 mmol, 87% yield).

Rf $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (80/20, v/v): 0.44. ^1H NMR (400 MHz, CDCl_3): δ 7.44 – 7.31 (m, 5H, CH_{Ar}), 7.12 (d, $J = 8.5$ Hz, 2H, CH_{Ar}), 6.92 (d, $J = 8.6$ Hz, 2H, CH_{Ar}), 5.04 (s, 2H, CCH_2Ph), 4.72 (d, $J = 5.1$ Hz, 1H, NH), 3.82 (s, 1H, CHNH), 3.67 (ddd, $J = 15.3, 10.2, 4.5$ Hz, 2H, CHCH_2Ph), 2.78 (d, $J = 7.1$ Hz, 2H, CH_2OH), 2.36 (s, 1H, OH), 1.42 (s, 9H, 3 CH_3 , Boc). Data in accordance with the literature.^{14, 15}

(S)-(1-(4-(Benzyloxy)phenyl)-3-hydroxypropan-2-yl)amine (8)

The protocol was adapted from Mavridis *et al.*¹⁶ The protected amino alcohol **7** (1.60 g, 4.48 mmol, 1 eq.) was dissolved in anhydrous CH_2Cl_2 (12.5 mL/mmol) under argon atmosphere. Trifluoroacetic acid (4.15 mL/mmol) was added and the reaction mixture was stirred for 1 h at room temperature. After concentration *in vacuo*, the resulting crude product was purified by silica gel flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the title compound as a white solid (1.57 g, 4.23 mmol, 94%).

Rf $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (97.5/2.5 v/v): 0.25. ^1H NMR (400 MHz, MeOD): δ 7.46 – 7.26 (m, 5H, CH_{Ar}), 7.19 (d, $J = 8.6$ Hz, 2H, CH_{Ar}), 6.98 (d, $J = 8.7$ Hz, 2H, CH_{Ar}), 5.08 (s, 2H, CCH_2Ph), 3.68 (dd, $J = 11.6, 3.5$ Hz, 1H, CHCH_2Ph), 3.51 (dd, $J = 11.6, 6.2$ Hz, 1H, CHCH_2Ph), 3.35 – 3.41 (m, 1H, CHCH_2Ph), 2.94 – 2.78 (m, 2H, CH_2OH). Data in accordance with the literature.¹⁶

Benzy (S)-(1-(4-(benzyloxy)phenyl)-3-hydroxypropan-2-yl) carbamate (9)

The protocol was adapted from Veitia *et al.*¹⁷ The amino alcohol salt **8** (0.80 g, 3.11 mmol, 1 eq.) was dissolved in CH_2Cl_2 (3.3 mL/mmol) at 0°C . Et_3N (1 eq.) was added dropwise and the reaction mixture was stirred for 15 min. Benzy chloroformate (1.2 eq.) and additional Et_3N (5 eq.) were added dropwise at 0°C . The resulting mixture was stirred at room temperature for 4.5 h. After concentration, the resulting crude product was purified by silica gel flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the title compound as a white powder (354 mg, 0.904 mmol, 29%). Rf $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95/5 v/v): 0.74. ^1H NMR (400 MHz, CDCl_3): δ 7.48 – 7.28 (m, 10H, CH_{Ar}), 7.11 (d, $J = 8.1$ Hz, 2H, CH_{Ar}), 6.90 (d, $J = 8.4$ Hz, 2H, CH_{Ar}), 5.08 (s, 2H, OCH_2Ph), 5.04 (s, 2H, OCH_2Ph), 4.97 (d, $J = 7.0$ Hz, 1H, NH), 3.90 (s, 1H, CHNH), 3.68 (d, $J = 10.1$ Hz, 1H, CCH_2Ph), 3.58 (d, $J = 10.3$ Hz, 1H, CCH_2Ph), 2.80 (d, $J = 7.0$ Hz, 2H, CH_2OH), 2.17 (s, 2H, OH). Data in accordance with the literature.¹⁷

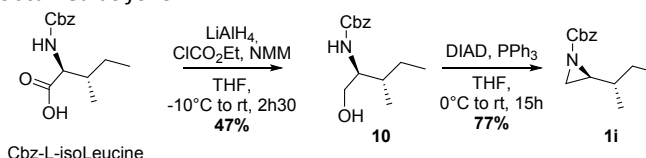
Benzy (S)-2-(4-(benzyloxy)benzyl)aziridine-1-carbamate (1e)

The *N*-Cbz-amino alcohol **9** (350 mg, 0.894 mmol, 1 eq.) was dissolved under argon atmosphere in anhydrous THF (13.2 mL/mmol) at 0°C . Triphenylphosphine (1.5 eq.) was added in one portion, followed by diisopropyl azodicarboxylate (1.64 eq.)

dropwise at 0°C . The reaction mixture was stirred for 21 h at room temperature. After concentration, the resulting crude product was purified by silica gel flash chromatography (petroleum ether/ EtOAc) to afford the title compound as a white solid (291 mg, 779 mmol, 87%).

Rf petroleum ether/ EtOAc (9/1 v/v): 0.25. ^1H NMR (500 MHz, CDCl_3): δ 7.50 – 7.28 (m, 10H, CH_{Ar}), 7.20 (d, $J = 8.5$ Hz, 2H, CH_{Ar}), 6.92 (d, $J = 8.5$ Hz, 2H, CH_{Ar}), 5.12 (q, 2H, $\text{OCH}_2\text{Ph}_{\text{Cbz}}$), 5.04 (s, 2H, OCH_2Ph), 2.92 (dd, $J = 13.6, 4.9$ Hz, 1H, CH_2Ph), 2.75 – 2.58 (m, 2H, CH_2Ph , CH_{Az}), 2.39 (d, $J = 5.6$ Hz, 1H, $\text{CH}_{2,\text{Az}}$), 2.09 (d, $J = 3.4$ Hz, 1H, $\text{CH}_{2,\text{Az}}$). ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 163.4 (s, $\text{C}(\text{O})\text{Cbz}$), 157.7 (s, CO), 137.1 (s, C_{Ar}), 135.8 (s, C_{Ar}), 130.0 (s, CH_{Ar}), 128.7 (s, CH_{Ar}), 128.6 (s, CH_{Ar}), 128.4 (s, CH_{Ar}), 128.1 (s, CH_{Ar}), 128.1 (s, CH_{Ar}), 127.6 (s, CH_{Ar}), 114.9 (s, CH_{Ar}), 70.1 (OCH_2Ph), 68.2 (s, $\text{O}(\text{O})\text{CH}_2\text{Ph}$), 38.9 (s, CH_{Az}), 37.5 (s, CH_2), 31.6 (s, CH_2Az). HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_3$ 374.1751; found 374.1755.

Benzy (S)-2-((S)-sec-butyl)aziridine-1-carbamate (**1i**) was obtained as follow:



Benzy (S)-2-((S)-sec-butyl)-2-hydroxyethyl-carbamate (10)

The Cbz-L-Isoleucine-OH (2.0 g, 7.54 mmol, 1 eq.) was dissolved in anhydrous THF (2.3 mL/mmol) under argon atmosphere. *N*-Methyl morpholine (1 eq.) and ethyl chloroformate (1 eq.) were added at -10°C , and the reaction mixture was stirred for 30 min at -10°C . LiAlH_4 (2.01 eq.) was then slowly added dropwise, and the reaction was allowed to warm at room temperature. The reaction mixture was stirred for 2.5 h and then quenched by the slow addition of an aqueous solution of KHSO_4 (1M) at 0°C . After being stirred for 15 min, the reaction mixture was filtered on a glass filter. The filtrate was concentrated, dissolved in ethyl acetate, and washed with NaCl saturated solution. The organic layer was dried over MgSO_4 , filtered, and concentrated *in vacuo*. The resulting crude was purified by silica gel flash chromatography (DCM/EtOAc) to afford the title compound as an oil (0.90 g, 3.58 mmol, 47% yield).

Rf petroleum ether/ EtOAc (7/3 v/v): 0.53. ^1H NMR (400 MHz, CDCl_3): δ 7.41 – 7.28 (m, 5H, CH_{Ar}), 5.10 (s, 2H, $\text{OCH}_2\text{Ph}_{\text{Cbz}}$), 4.93 (d, $J = 7.1$ Hz, 1H, NH), 3.74 (d, $J = 10.6$ Hz, 1H, NHCH), 3.69 – 3.52 (m, 2H, CH_2OH), 2.22 (s, 1H, OH), 1.64 – 1.56 (m, 1H, CH_2CH_3), 1.56 – 1.44 (m, 1H, CH_2CH_3), 1.15 (ddd, $J = 22.5, 15.0, 6.8$ Hz, 1H, CHMe_2), 1.02 – 0.72 (m, 6H, 2 CH_3). Data in accordance with the literature.¹⁸

Benzy (S)-2-((S)-sec-butyl)aziridine-1-carboxylate (1i)

The *N*-Cbz-amino alcohol **10** (0.80 g, 3.20 mmol, 1 eq.) was dissolved under argon atmosphere in anhydrous THF (13.2 mL/mmol) at 0°C . Triphenylphosphine (1.5 eq.) was added in one portion, followed by diisopropyl azodicarboxylate (1.64 eq.) dropwise at 0°C . The reaction mixture was stirred for 15 h at room temperature. After concentration, the resulting crude product was purified by silica gel flash chromatography

(petroleum ether/EtOAc) to afford the title compound as a light pink liquid (570 mg, 2.48 mmol, 77%).

Rf petroleum ether/EtOAc (8/2 v/v) : 0.72. ^1H NMR (500 MHz, CDCl_3) δ 7.40 – 7.35 (m, 4H, CHAr), 7.35 – 7.29 (m, 1H, CHAr), 5.13 (d, J = 1.0 Hz, 2H, OCH_2Ph), 2.31 (d, J = 6.3 Hz, 1H, CH_2Az), 2.27 (m, 1H, CHAz), 2.00 (d, J = 3.8 Hz, 1H, CH_2Az), 1.80 – 1.61 (m, 1H, CH_2), 1.41 – 1.31 (m, 1H, CH_2), 1.31 – 1.12 (m, 1H, CH), 0.96 (t, J = 7.5 Hz, 3H, CH_3CH_2), 0.91 (d, J = 6.9 Hz, 3H, CH_3CH_2). ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ 163.8 (s, $\text{C}(\text{O})\text{CH}_2\text{Ph,Cbz}$), 136.1 (s, CAr), 128.6 (s, CHAr), 128.3 (s, CHAr), 128.1 (CHAr), 68.1 (s, OCH_2Ph), 43.6 (s, CHAz), 37.7 (s, CHCH_3), 30.8 (s, CH_2Az), 27.7 (s, CH_2CH_3), 15.9 (CHCH_3), 11.2 (CH_2CH_3). HRMS (ESI/Q-TOF) m/z : [$\text{M} + \text{H}$] $^+$ Calculated for $\text{C}_{14}\text{H}_{20}\text{NO}_2$: 234.1489; found: 234.1490.

General procedure for the preparation of N-methylene-phosphonate aziridines from N-carbamoyl aziridines

Freshly distilled diethylphosphite (6.1 eq.) was dissolved in anhydrous THF (0.5 mL/mmol of diethylphosphite) under argon atmosphere. The solution was cooled to -78°C , then $n\text{-BuLi}$ (2.5M in THF, 6 eq.) was added dropwise and the reaction mixture was stirred for 30 min at -78°C . A solution of the N-carbamoyl aziridine (1 eq.) 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 the required temperature until completion of the reaction (TLC monitoring). The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl . The mixture was extracted twice with ethyl acetate. Organic layers were dried on MgSO_4 , filtered and concentrated in vacuum and the crude was purified on silica gel by flash chromatography (DCM/MeOH gradient) to obtain the desired product as an oil.

Diethyl (S)-((2-(2-(1H-benzo[d]imidazol-1-yl)ethyl)aziridin-1-yl)methyl)phosphonate (2a)

The title compound (146 mg, 0.43 mmol, 44%) was obtained following the procedure described above, overnight stirring at rt, from the compound **1a** (200 mg, 0.69 mmol). When the reaction was performed overnight stirring at 55°C , compound **2a** (189 mg, 0.56 mmol) was isolated with 54% yield from the compound **1a** (300 mg, 1.04 mmol).

Rf DCM/MeOH (95/5, v/v): 0.25. ^1H NMR (500 MHz, CDCl_3) δ 8.04 (s, 1H, NCHArN), 7.79 (dd, J = 6.5, 2.1 Hz, 1H, CHAr), 7.41 (dd, J = 7.0, 2.6 Hz, 1H, CHAr), 7.30 – 7.24 (m, 2H, CHAr), 4.39 (tdd, J = 14.2, 11.0, 6.6 Hz, 2H, CH_2N), 4.21 – 4.10 (m, 4H, $2\text{CH}_2\text{CH}_3$), 2.84 (t, J = 14.5 Hz, 1H, CH_2P), 2.40 (dd, J = 14.5, 12.1 Hz, 1H, CH_2P), 2.10 (dtd, J = 12.3, 7.7, 4.7 Hz, 1H, $\text{CH}_2\text{CH}_2\text{N}$), 1.83 (dtd, J = 13.1, 7.4, 5.7 Hz, 1H, $\text{CH}_2\text{CH}_2\text{N}$), 1.63 (dd, J = 3.6, 1.1 Hz, 1H, CH_2 , Az), 1.53 – 1.47 (m, 1H, CHAz), 1.37 (dd, J = 6.5, 1.0 Hz, 1H, CH_2 , Az), 1.33 (q, J = 7.0 Hz, 6H, $2\text{CH}_2\text{CH}_3$). ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ 144.0 (s, CAr), 143.4 (s, NCHN), 133.8 (s, CAr), 122.9 (s, CHAr), 122.2 (s, CHAr), 120.5 (s, CHAr), 109.7 (s, CHAr), 62.3 (dd, J = 35.8, 7.1 Hz, 2C, $2\text{CH}_2\text{CH}_3$), 56.0 (d, J = 160.4 Hz, CH_2P), 43.1 (s, CH_2N), 38.3 (d, J = 7.3 Hz, CHAz), 34.7 (d, J = 13.1 Hz, CH_2 , Az), 33.2 (s, $\text{CH}_2\text{CH}_2\text{N}$), 17.3 – 16.0 (t, J = 6.3 Hz, 2C, $2\text{CH}_2\text{CH}_3$). ^{31}P { ^1H } NMR (202 MHz, CDCl_3) δ 23.6 (s). HRMS Q-TOF (ESI) [$\text{M} + \text{H}$] $^+$, Calculated for $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_3\text{P}$: 338.1634; found: 338.1633.

Diethyl (S)-((2-benzylaziridin-1-yl)methyl)phosphonate (2b)

The title compound (93 mg, 0.33 mmol, 51%) was obtained following the procedure described above, stirring for 2 h at 55°C , from the compound **1b** (150 mg, 0.64 mmol). Starting from the compound **1c** (150 mg, 0.56 mmol), compound **2b** (126 mg, 0.44 mmol) was isolated with 43% yield. When stirring for 5 h at rt, compound **2b** (100 mg, 0.35 mmol) was isolated with 45% yield from **1c** (170 mg, 0.63 mmol).

Rf DCM/MeOH (95/5, v/v): 0.50. ^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.19 (m, 5H, CHAr), 4.21 – 4.13 (m, 4H, $2\text{CH}_2\text{CH}_3$), 2.97 (dd, J = 14.4, 5.6 Hz, 1H, CH_2Ph), 2.69 (ddd, J = 37.8, 14.5, 13.4 Hz, 2H, CH_2P), 2.55 (dd, J = 14.4, 6.7 Hz, 1H, CH_2Ph), 1.81 (dd, J = 3.8, 0.8 Hz, 1H, CH_2 , Az), 1.76 – 1.70 (m, 1H, CHAz), 1.45 – 1.42 (dd, J = 4, 1.5 Hz, 1H, CH_2 , Az), 1.35 (td, J = 7.1, 3.7 Hz, 6H, $2\text{CH}_2\text{CH}_3$). ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ 139.3 (s, CAr), 128.9 (s, 2C, CHAr), 128.5 (s, 2C, CHAr), 126.4 (s, CHAr), 62.2 (d, J = 8.3 Hz, 2C, $2\text{CH}_2\text{CH}_3$), 56.1 (d, J = 159.8 Hz, CH_2P), 42.0 (d, J = 10.8 Hz, CHAz), 39.1 (s, CH_2Ph), 35.3 (d, J = 10.6 Hz, CH_2 , Az), 16.7 (d, J = 7.8 Hz, 2C, $2\text{CH}_2\text{CH}_3$). ^{31}P { ^1H } NMR (202 MHz, CDCl_3) δ 23.9 (s). HRMS Q-TOF (ESI) [$\text{M} + \text{H}$] $^+$ Calculated for $\text{C}_{14}\text{H}_{23}\text{NO}_3\text{P}$: 284.1410; found: 284.1413.

Diethyl (S)-((2-(4-(benzyloxy)benzyl)aziridin-1-yl)methyl)phosphonate (2d)

The title compound (60 mg, 0.15 mmol, 52% yield) was obtained following the procedure described above, stirring for 4 h at 55°C , from the compound **1d** (100 mg, 0.29 mmol). Starting from compound **1e** (298 mg, 0.798 mmol), compound **2d** (115 mg, 0.295 mmol) was isolated with 38% yield.

Rf DCM/MeOH (95/5, v/v): 0.50. ^1H NMR (600 MHz, CDCl_3) δ 7.44 – 7.41 (m, 2H, CHAr), 7.40 – 7.36 (m, 2H, CHAr), 7.33 – 7.31 (m, 1H, CHAr), 7.15 (d, J = 8.5 Hz, 2H, CHAr), 6.90 (d, J = 8.6 Hz, 2H, CHAr), 5.04 (s, 2H, OCH_2Ph), 4.20 – 4.13 (m, 4H, $2\text{CH}_2\text{CH}_3$), 2.90 (dd, J = 14.4, 5.6 Hz, 1H, CHCH_2Ph), 2.68 (ddd, J = 41.2, 14.6, 13.4 Hz, 2H, CH_2P), 2.50 (dd, J = 14.4, 6.7 Hz, 1H, CHCH_2Ph), 1.79 (dd, J = 3.5, 1.0 Hz, 1H, CH_2 , Az), 1.77 – 1.72 (m, 1H, CHAz), 1.42 (dd, J = 6.3, 0.7 Hz, 1H, CH_2 , Az), 1.35 (td, J = 7.0, 4.2 Hz, 6H, $2\text{CH}_2\text{CH}_3$). ^{13}C { ^1H } NMR (151 MHz, CDCl_3) δ 157.6 (s, CAr), 137.3 (s, CAr), 131.7 (s, CAr), 129.9 (s, 2C, CHAr), 128.7 (s, 2C, CHAr), 128.1 (s, CHAr), 127.6 (s, 2C, CHAr), 114.9 (s, 2C, CHAr), 70.2 (s, OCH_2Ph), 62.2 (d, J = 8.9 Hz, 2C, $2\text{CH}_2\text{CH}_3$), 56.1 (d, J = 159.7 Hz, CH_2P), 42.2 (d, J = 10.9 Hz, CHAz), 38.2 (s, CHCH_2Ph), 35.2 (d, J = 10.8 Hz, CH_2 , Az), 16.7 (d, J = 7.6 Hz, 2C, CH_2CH_3). ^{31}P { ^1H } NMR (162 MHz, CDCl_3) δ 24.2 (s). HRMS Q-TOF (ESI) [$\text{M} + \text{H}$] $^+$ Calculated for $\text{C}_{21}\text{H}_{29}\text{NO}_4\text{P}$: 390.1834; found: 390.1833.

Diethyl (S)-((2-((1H-indol-3-yl)methyl)aziridin-1-yl)methyl)phosphonate (2f)

The title compound (35 mg, 0.11 mmol, 28%) was obtained following the procedure described above, stirring for 2 h at 55°C , from the compound **1f** (120 mg, 0.39 mmol) and contained traces of the corresponding bis-phosphonate. Both sets of NMR signals are reported below.

Rf DCM/MeOH (95/5, v/v): 0.4. ^1H NMR (500 MHz, CDCl_3) δ 8.24 (s, 1H, NH), 7.65 (d, J = 7.9 Hz, 1H, CHAr), 7.61 (d, J = 7.6 Hz, 0.42H, CH'Ar), 7.36 (d, J = 8.1 Hz, 1H, CHAr), 7.36 (d, J = 7.2 Hz, 0.32, CH'Ar), 7.21 – 7.16 (m, 1H, CHAr), 7.19 – 7.16 (m, 0.41H, CH'Ar), 7.13 – 7.09 (m, 1H, CHAr), 7.10 (t, J = 7.8 Hz, 0.38H, CH'Ar), 7.07 (d, J = 2.2 Hz, 1H, CHAr), 7.03 (d, J = 2.3 Hz, 0.37H,

CH'Ar), 4.32 – 4.22 (m, 2.46H, 4CH₂CH₃), 4.21 – 4.14 (m, 4H, 4CH₂CH₃), 3.51 (dd, J = 14.9, 3.7 Hz, 0.54H, CH'CH₂C), 3.11 (dd, J = 15.0, 5.4 Hz, 1H, CHCH₂C), 2.80 – 2.61 (m, 3H, CH₂P, CHCH₂C), 2.52 (dd, J = 14.8, 9.0 Hz, 1H, CHCH₂C), 2.43 (t, J = 18.2 Hz, 0.52H, PCH'P), 2.19 – 2.12 (m, 0.49H, CH'Az), 1.97 (d, J = 3.8 Hz, 0.48H, CH₂, Az), 1.86 (dd, J = 3.8, 0.8 Hz, 1H, CH₂, Az), 1.83 – 1.78 (m, 1H, CHAz), 1.73 (d, J = 6.1 Hz, 0.43H, CH₂, Az), 1.45 (d, J = 6.3 Hz, 1H, CH₂, Az), 1.35 (td, J = 7.0, 2.8 Hz, 8.3H, 2CH₂CH₃, 2CH₂CH₃). ¹³C {1H} NMR (126 MHz, CDCl₃) δ 136.4 (s, CAr), 127.7 (s, CAr), 122.1 (s, CHAr), 122.0 (s, CHAr) 119.4 (s, CHAr), 119.2 (s, CHAr), 113.5 (s, CAr), 111.2 (s, CHAr), 65.0 (t, J = 150 Hz, PCHP), 63.2 (dd, J = 24.0, 5.9 Hz, 4C, 4CH₂CH₃), 62.3 (t, J = 7.3 Hz, 2C, 2CH₂CH₃), 56.1 (d, J = 159.6 Hz, CH₂P), 42.8 (d, J = 16.3 Hz, CHAz), 41.7 (d, J = 10.3 Hz, CHAz), 37.0 (d, J = 16.9 Hz, CH₂, Az), 35.7 (d, J = 9.8 Hz, CH₂, Az), 28.9 (s, CHCH₂C), 28.6 (s, CHCH₂C), 16.7 (d, J = 7.2 Hz, 2C, 2CH₂CH₃). ³¹P {1H} NMR (202 MHz, CDCl₃) δ 24.2 (s), 18.1 (s'). HRMS Q-TOF (ESI) [M+H]⁺ Calculated for C₁₆H₂₄N₂O₃P: 323.1525; found: 323.1525.

Diethyl (((S)-2-((S)-sec-butyl)aziridin-1-yl)methyl)phosphonate (2h)

The title compound was obtained following the procedure described above, stirring for 2 h at 55°C, from the compound **1h** (150 mg, 0.75 mmol) with 53% yield (99 mg, 0.39 mmol). When using compound **1i** (300 mg, 1.286 mmol) as starting material, stirring for 4 h at 55°C, compound **2h** (79 mg, 0.317 mmol) was isolated with 25% yield.

Rf DCM/MeOH (95/5, v/v): 0.5. ¹H NMR (500 MHz, CDCl₃): δ 4.25 – 4.09 (m, 4H, OCH₂Et), 2.85 – 2.73 (m, 1H, CH₂Az), 2.53 (dd, J = 14.6, 12.8 Hz, 1H, CH₂Az), 1.67 (dd, J = 3.8, 0.9 Hz, 1H, CH₂P), 1.66 – 1.59 (m, 1H, CH₂), 1.34 (td, J = 7.0, 3.6 Hz, 7H, 2CH₃Et, CH, Az), 1.32 – 1.21 (m, 2H, CH₂, CHP), 1.15 – 1.02 (m, 1H, CH), 0.91 (t, J = 7.5 Hz, 3H, CH₃CH₂), 0.84 (d, J = 6.9 Hz, 3H, CH₃CH). ¹³C {1H} NMR (126 MHz, CDCl₃): δ 62.2 (dd, J = 10.7, 6.6 Hz, 2CH₂Et), 56.37 (d, J = 159.5 Hz, CH₂Az), 46.89 (d, J = 10.5 Hz, CH₂), 37.97 (s, CH), 34.21 (d, J = 8.2 Hz, CH, Az), 28.06 (s, CH₂P), 16.64 (t, J = 5.0 Hz, 2CH₂CH₃Et), 16.17 (s, CH₃CH₂), 11.58 (s, CH₃CH). ³¹P {1H} NMR (162 MHz, CDCl₃): δ 24.4 (s). HRMS Q-TOF (ESI) [M+H]⁺ Calculated for C₁₁H₂₅NO₃P: 250.1567; found: 250.1566.

tert-Butyl (S)-4-(1-((diethoxyphosphoryl)methyl)aziridin-2-yl)butyl)carbamate (2j)

The title compound (57 mg, 0.15 mmol, 45%) was obtained following the procedure described above, stirring for 4 h at 55°C, from the compound **1j** (120 mg, 0.35 mmol).

Rf DCM/MeOH (95/5, v/v): 0.18. ¹H NMR (600 MHz, CDCl₃) δ 4.75 (br s, 1H, NH), 4.19 – 4.10 (m, 4H, 2CH₂CH₃), 3.10 – 3.04 (m, 2H, CH₂NH), 2.72 (t, J = 14.1 Hz, 1H, CH₂P), 2.53 (t, J = 13.6 Hz, 1H, CH₂P), 1.62 (d, J = 2.0 Hz, 1H, CH₂, Az), 1.55 – 1.42 (m, 8H, CH₂, Az, 3CH₂, CHAz), 1.40 (s, 9H, 3CH₃, Boc), 1.32 (dt, J = 8.7, 7.1 Hz, 6H, 2CH₂CH₃). ¹³C {1H} NMR (151 MHz, CDCl₃) δ 156.1 (s, NHC(O)O), 79.0 (s, C(CH₃)₃), 62.2 (dd, J = 26.5, 7.1 Hz, 2C, 2CH₂CH₃), 56.3 (d, J = 159.9 Hz, CH₂P), 41.0 (d, J = 8.7 Hz, CHAz), 40.3 (s, CH₂NH), 35.3 (d, J = 11.7 Hz, CH₂, Az), 32.5 (s, CH₂), 29.7 (s, CH₂), 28.5 (s, 3C, 3CH₃, Boc), 24.5 (s, CH₂), 18.5 – 15.5 (m, 2C, 2CH₂CH₃). ³¹P {1H} NMR (162 MHz, CDCl₃) δ 24.0 (s). HRMS Q-TOF (ESI) [M+H]⁺ Calculated for C₁₆H₃₄N₂O₅P: 365.2205; found: 365.2211.

Diethyl (((1R,6S)-7-azabicyclo[4.1.0]heptan-7-yl)methylene)phosphonate (2l)

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The title compound (254 mg, 1.028 mmol, 47%) was obtained following the procedure described above, stirring for 4 h at 55°C, from the compound **1l** (500 mg, 2.162 mmol).

Rf Petroleum ether/acetone (7/3, v/v): 0.82. ¹H NMR (500 MHz, CDCl₃): δ 4.27 – 4.10 (m, 4H, 2CH₂CH₃), 2.65 (dd, J = 13.0, 2.3 Hz, 2H, 2CH₂Az), 1.88 – 1.78 (m, 2H, CH₂CH), 1.71 (s, 2H, CH₂CH), 1.61 (s, 2H, CH₂P), 1.33 (td, J = 7.0, 2.3 Hz, 8H, 2CH₃, CH₂), 1.19 – 1.05 (m, 2H, CH₂). ¹³C {1H} NMR (126 MHz, CDCl₃): δ 62.26 (d, J = 6.6 Hz, 2CH₂O), 55.92 (d, J = 158.7 Hz, 2CH₂Az), 39.87 (d, J = 9.7 Hz, CH₂P), 24.13 (s, 2CH₂CH), 20.44 (s, 2CH₂), 16.63 (d, J = 5.7 Hz, 2CH₃). ³¹P {1H} NMR (162 MHz, CDCl₃) δ 24.5 (s). HRMS Q-TOF (ESI) [M+H]⁺ Calculated for C₁₁H₂₃NO₃P: 248.1410; found: 248.1414.

(1aR,6aS)-1,1a,6,6a-Tetrahydroindeno[1,2-b]azirine (2m)

The title compound (48 mg, 0.37 mmol, 84%) was obtained following the procedure described above, stirring for 6 h at 55°C, from the compound **1m** (100 mg, 0.44 mmol). Data in accordance with the literature.¹²

Conclusions

It has been shown that *N*-carbamoyl aziridines may be converted into methylene-*gem*-bisphosphonylated or methylene phosphonylated derivatives under similar conditions where the outcome depends on the choice of the lithiated base. To our knowledge, these are the first reports of this type of synthetic strategy. A broad range of *N*-Cbz and *N*-Boc aziridines was used to study the scope of this reaction, which afforded the desired phosphonylated compounds in low to moderate yields. The substrate scope of the reaction, combined with the isolation and identification of by-products, and additional spectroscopic analyses, has led to a possible mechanism. This mechanism requires lithium ion, a strong nucleophilic base and the presence of the aziridine ring to produce *N*-methylene phosphonate aziridines.

Author Contributions

Author contributions were as follow: I.G. (Investigations), T.C. (Investigations, conceptualization and writing original draft preparation), S.P. (Conceptualization, supervision, writing, review and editing, and funding acquisition).

Conflicts of interest

There are no conflicts to declare.

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