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Palladium-catalyzed allylic substitution between C-based nucleophiles and 6-azabicyclo[3.1.0]-hex-3-en-2-oxy derivatives: A new selectivity paradigm

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The reaction between α -hydroxy-(or α -acetoxy) cyclopenten-aziridines (6-azabicyclo[3.1.0]hex-3-en-2-ols or acetates) and C-based nucleophiles in the presence of Pd(0)-catalysis was investigated. In all the cases studied, the reaction was totally regio- and diastereo-selective, affording a single adduct in moderate to good yields. Specifically, attack of the nucleophile at position 3 of the cyclopentene moiety, *anti* to the vicinal oxy group, with vinylogous ring opening of the aziridine ring, was observed. When the carbon acid is a very acidic methylene ($pK_a(\text{DMSO}) \leq 7.3$), the resulting adduct is a zwitterion, resulting from an intramolecular proton transfer between the amino group and the carbon acid moiety taking place after the C–C bond formation. A plausible mechanism for this transformation is put forward.

1. Introduction

Aziridines are the smallest members of the aza-heterocycle family [1,2]. Due to their considerable ring strain, these molecules show in general a high reactivity that makes them major intermediates for organic synthesis. Furthermore, several biologically active natural products [3], or analogs of them, incorporate the aziridine motif.

In 1972, Kaplan et al. [4] reported an interesting photochemical conversion of *N*-alkylpyridinium salts, such as **A**, into the corresponding α -hydroxycyclopenten-aziridines (6-aza-bicyclo[3.1.0]hex-3-en-2-ol) such as **D** (Scheme 1). The mechanism of this photoelectrocyclization involves a $\pi \rightarrow \pi^*$ transition of the aromatic nucleus, followed by the transient generation of the 6-aza[3.1.0]

bicyclic allylic cation **B**, in equilibrium with the corresponding azoniabenzvalene cation **C**. Subsequent *in situ* interception by the water (or alcohol) solvent from the least hindered face affords the α -hydroxycyclopenten-aziridines **D** photoproduct.

The potential of this seminal work remained unexploited for a decade, until Mariano [5] found that *in situ* solvolytic opening of the α -oxycyclopenten-aziridines photoproduct can take place regio- and stereospecifically in a S_N2 mode. Since the global transformation provided a cyclopentene motif with total *trans* control at C3/C4 and C4/C5 (Scheme 2), the relevance of this method for the synthesis of aminocyclitols was immediately apparent.

Subsequently, several groups, including those of Mariano [6–8], Burger [9–12], Ganem [13] and Penkett [14–16] revisited and extended the scope of this chemistry, achieving synthetically important targets such as (+)-mannostatin A [17], (+)-castanospermine [18], (–)-swainsonine [19], the aminocyclopentitol cores of allosamidine [20], trehazolin [21] and 3-amino-3-deoxy sugars [22–28]. More recently, we contributed to this topic, by accomplishing the generation and the subsequent ring opening of the resulting α -oxycyclopenten-aziridines in water at physiological pH using heteroatom-based nucleophiles, including the peptide hormone salmon calcitonin (sCT) [29], and by performing the photoelectrocyclization/nucleophilic interception sequence using different home-made continuous UV-light photoflow reactors

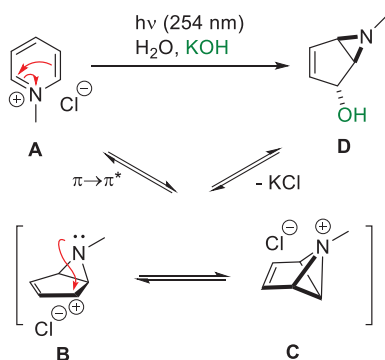
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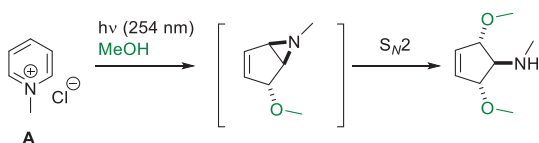
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Scheme 1. Kaplan's pioneering studies: photochemical conversion of 1-methylpyridinium-1-ium chloride **A** into α -hydroxycyclopenten-aziridine **D** [4].

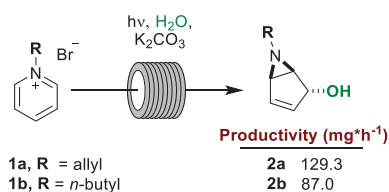


Scheme 2. Photochemical electrocyclicization of N-methyl-pyridinium chloride followed by methanolytic α -oxy-cyclopenten-aziridine opening [5].

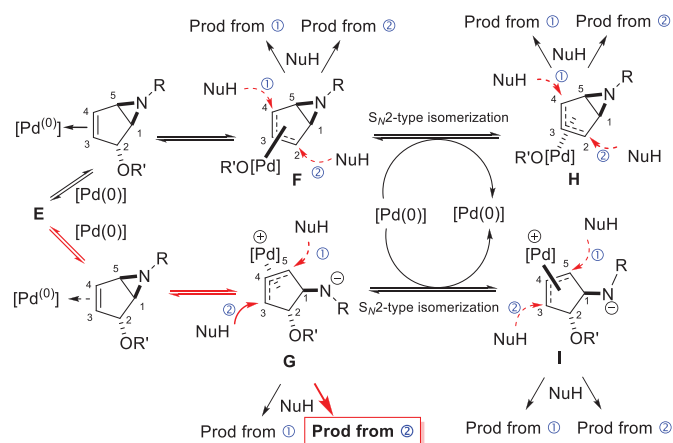
[30,31]. Our process allowed the production of α -hydroxycyclopenten-aziridines in gram scale, e.g. 1.9 g of 6-allyl-6-azabicyclo[3.1.0]hex-3-en-2-ol (**2a**) and 1.8 g of 6-butyl-6-azabicyclo[3.1.0]hex-3-en-2-ol (**2b**), increasing the process productivity regarding to the reported batch process, namely: 3:1 for **2a** [32] (129.3 $mg\ h^{-1}$ vs 39.4 $mg\ h^{-1}$) and 18:1 for **2b** [29] (87.0 $mg\ h^{-1}$ vs 4.8 $mg\ h^{-1}$) (Scheme 3).

Considering the peculiar structure of the above described α -oxy-cyclopenten-aziridines in connection with our long-standing interest in Pd-catalyzed allylations [33–36], we were intrigued by the thought of investigating the behavior of such cyclic substrates against soft carbon-based pro-nucleophiles under Pd(0) catalysis. In particular, we reasoned that such an approach could have opened the way to a hitherto unexplored C–C functionalization of α -oxy-cyclopenten-aziridines.

Some preliminary considerations are worthy, before presenting the results. The cyclopentene motif in these α -oxy-cyclopenten-aziridines **E** is bis-allylically substituted, one allylic position being occupied by an oxy (alcohol, ether or ester) function, the other one being substituted with the *trans* C–N bond making part of the fused aziridine. In view of the known *anti* approach of a Pd(0) complex to an allylic leaving group, the initial generation of two alternative η^3 -allylpalladium complexes **F** and **G** may be expected, depending on the allylic group that prefers to leave. Furthermore, the known isomerization of η^3 -allylpalladium complexes via S_N2 type substitution [35] may allow generation of intermediates **H** and/or **I** prior of the nucleophilic trapping. Finally, each of the four η^3 -



Scheme 3. Process intensification for the synthesis of α -hydroxycyclopenten-aziridines using continuous UV-light photoflow home-made reactors [29,31].



Scheme 4. Potential regio- and stereo-selectivities in the Pd(0)-catalyzed allylic substitution between α -oxy-cyclopenten-aziridines and carbon-based soft nucleophiles. In red the experimentally observed reactivity from **G**. Brackets around palladium atom in a charged or neutral complex intend to render implicit the dative ligands.

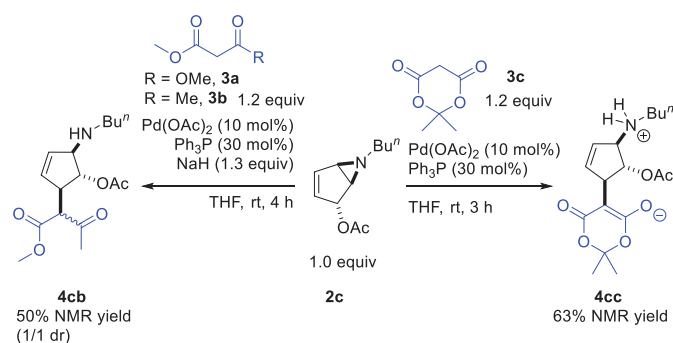
allylpalladium complexes **F**, **G**, **H** and **I** may in principle give rise to two regioisomers. As a result, prediction of product selectivity in this reaction is far from being straightforward (Scheme 4).

In the event, the Pd(0)-catalyzed reaction between C-based soft nucleophiles and α -hydroxycyclopenten-aziridines or acetates took constantly place in a totally regio- and diastereo-selective way, generating a single aminocyclopentene structure resulting from attack of the carbon nucleophile at C3 of intermediate **G** (Scheme 4), *anti* to the vicinal oxy group, with vinylogous aziridine opening.

2. Results/Discussion

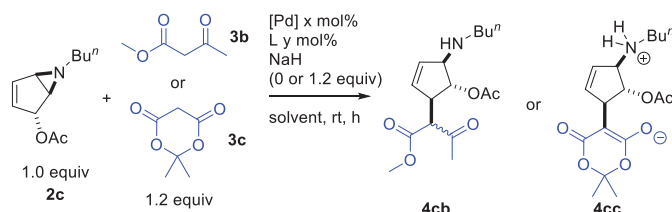
2.1. Optimization of the reaction conditions

Dimethyl malonate **3a** ($pK_a(H_2O) = 13$; $pK_a(DMSO) = 15.9$), methyl acetoacetate **3b** ($pK_a(H_2O) = 11$) and Meldrum's acid **3c** ($pK_a(H_2O) = 5$; $pK_a(DMSO) = 7.3$) were first considered as C-based pro-nucleophiles for the reaction with α -acetoxy-cyclopenten-aziridine **2c**, in turn obtained by standard acetylation of **2b**. As to the catalyst, we opted for the system $[Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%)] with or without NaH, in THF (Scheme 5) [37]. Dimethyl malonate **3a** gave no reaction, whether with or without a base, whereas methyl acetoacetate **3b** displayed a modest reactivity when working in the presence of 1.2 equiv of NaH (**4cb**, 50% NMR yield). In contrast, Meldrum's acid **3c** afforded aminocyclopentene **4cc** in 63% NMR yield under base free conditions. The above results suggest that the acidity of the activated methylene of the nucleophile has to fit in an



Scheme 5. Preliminary allylic substitution tests between dimethyl malonate **3a**, methyl acetoacetate **3b** or Meldrum's acid **3c** and α -acetoxy-cyclopenten-aziridine **2c**.

Table 1
Optimization of the reaction between methyl acetoacetate **3b** or Meldrum's acid **3c** with α -acetoxy-cyclopenten-aziridine **2c**.^a



Entry	NuH	[Pd] (x)	L (y)	Solvent (h)	Product, yield % ^b
1	3b	Pd(OAc) ₂ (10)	PPh ₃ (30)	THF (4)	4cb , 50
2	3b	Pd(OAc) ₂ (10)	dppe (20)	THF (18)	4cb , 41
3	3b	Pd(OAc) ₂ (10)	dppf (20)	THF (18)	4cb , 32
4	3b	Pd(OAc) ₂ (10)	MeDCHB (30)	THF (18)	4cb , 49
5	3b	[Pd(C ₃ H ₅ Cl) ₂] (10)	dppe (20)	THF (18)	4cb , 8
6	3b	Pd(OAc) ₂ (10)	PPh ₃ (30)	Et ₂ O (4)	4cb , 59
7	3b	Pd(OAc) ₂ (10)	PPh ₃ (30)	DIOX (4)	4cb , 72
8	3b	Pd(OAc)₂ (5)	PPh₃ (5)	DIOX (18)	4cb , 74
9	3c	Pd(OAc) ₂ (10)	PPh ₃ (30)	THF (3)	4cc , 63
10	3c	Pd(OAc) ₂ (10)	PPh ₃ (30)	DIOX (1.5)	4cc , 73
11	3c	Pd(OAc) ₂ (10)	PPh ₃ (30)	Et ₂ O (3.5)	4cc , 84
12	3c	Pd(OAc)₂ (5)	PPh₃ (15)	Et₂O (5)	4cc , 88

^a Reaction conditions: **2c** (1.0 equiv), **3b** or **3c** (1.2 equiv), solvent (0.5 M), NaH (1.2 equiv: entry 1 to 8, or 0 equiv: entry 9 to 12).

^b Determined by ¹H NMR analysis of the crude product using 1,4-dinitrobenzene as internal standard. DIOX: 1,4-dioxane; Dppe: 1,2-bis(diphenylphosphino)ethane; dppf: 1,1'-ferrocenediyl-bis(diphenylphosphine), MeDCHB: 2-dicyclohexylphosphino-2'-methylbiphenyl.

appropriate pK_a window to allow the allylic substitution to take place (Scheme 5).

The influence of the nature of the palladium catalyst, the ligand as well as the solvent were investigated next. The results are presented in Table 1.

In the reaction between methyl acetoacetate **3b** and the α -acetoxy-cyclopenten-aziridine **2c** in presence of NaH, the use of phosphines other than PPh₃ (mono- or bidentate) did not allow further improvements (Table 1, entries 1–4). Switch to {[Pd(η^3 -C₃H₅Cl)₂] (10 mol%)/dppe (20 mol%)} as catalytic system led to an important yield drop (Table 1, entry 5). Variation of the solvent was next addressed. While use of Et₂O led to an NMR yield essentially comparable to that of the experiment in THF (Table 1, entries 6 and 1), 1,4-dioxane significantly increased this result (Table 1, entry 7). Finally, the catalytic loading could be reduced to [Pd(OAc)₂ (5 mol%)/PPh₃ (15 mol%)] in 1,4-dioxane, without a significant yield erosion of the product **4cb** (Table 1, entry 8). Control experiments carried out by omitting the Pd source as well as the ligand afforded no trace of product **4**, giving mainly recovered starting materials, which confirmed the need of the catalytic system for the allylic substitution (see SI).

The influence of the solvent was also studied for the reaction with Meldrum's acid **3c** under base free conditions (Table 1, entries 9–11). In this case, use Et₂O afforded **4cc** as the sole product in 84% NMR yield (Table 1, entry 11). Here again, the loading of the catalytic system could be reduced to [Pd(OAc)₂ (5 mol%)/PPh₃ (15 mol%)] recording even a slight yield increase (Table 1, entry 12).

2.2. Scope of the reaction

With the optimized reaction conditions in hand, we passed to evaluate the scope of this allylic substitution starting with the use of the base-free conditions associated to the more acidic active methylenes (Table 2). The reaction between the free alcohol aziridine **2b** and Meldrum's acid **3c** was also successful, affording the corresponding allylic product **4bc**, although its isolated yield was lower than that of the reaction starting from the corresponding

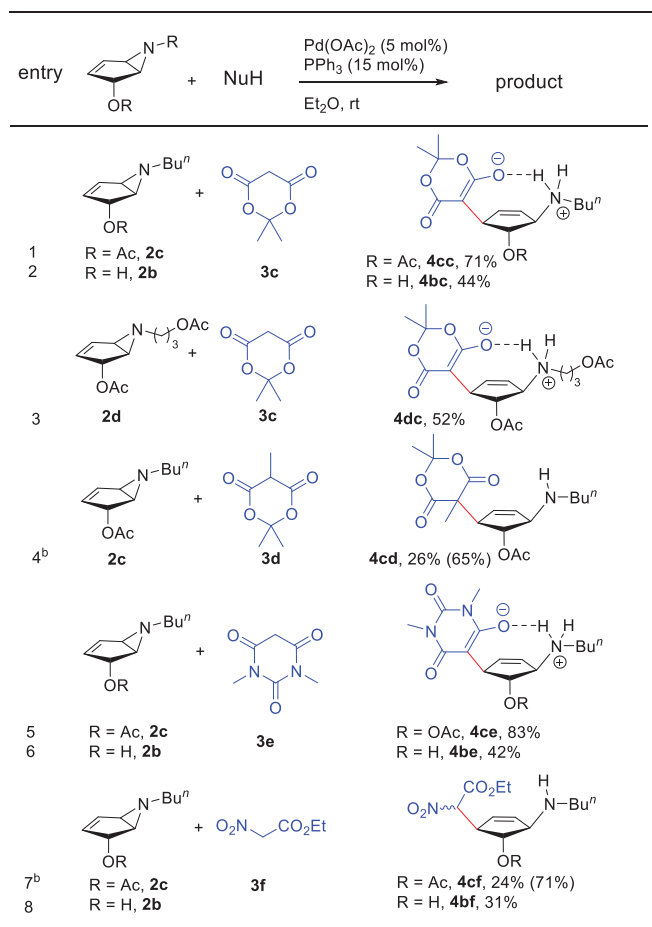
aziridine acetate **2c** (Table 2, compare entries 1 and 2). Use the α -acetoxy-cyclopenten-aziridine **2d** carrying a different substituent at the nitrogen atom gave with Meldrum's acid the expected product in fair yield of 52% (Table 2, entry 3). Reaction of the α -acetoxy-cyclopenten-aziridine **2c** with the methylated Meldrum's acid **3d** gave also the expected product **4cd**, although with a low yield. It should be noted that, in contrast to the previously obtained products, product **4cd** cannot stay as its inner salt form, due to the lack of a second acidic proton. This is also confirmed by the very inferior polarity of **4cd** with respect to that of the other substitution products. The reaction between *N,N*-dimethyl barbituric acid (pK_a (H₂O) = 4) and the α -acetoxy-cyclopenten-aziridine **2c** or the hydroxy derivative **2b**, paralleled the behavior observed with Meldrum's acid, giving in both cases the expected allylic substitution product with better yields in the case of the acetate partner (Table 2, compare entries 5 and 6). Finally, the two reactions could also be extended to ethyl nitroacetate (pK_a (H₂O) = 5.79; pK_a (DMSO) = 9.1) (Table 2, entries 7 and 8), although the corresponding products were obtained in a modest yield. At last, the dimedone, bearing also a very acidic methylene (pK_a (H₂O) = 5.2; pK_a (DMSO) = 11.2) was tested, but unfortunately led to an unanalyzable complex mixture.

We then evaluated the allylations of the less acidic active methylenes, which required the use of NaH as base. In the event, methyl acetoacetate **3b** reacted with the acetoxyaziridine **2c** as well as with the free alcohol **2b** to give the corresponding allylation products **4cb** [38] and **4bb** in 74% NMR yield and 65% isolated yield, respectively (Scheme 6). Finally, other less acidic active methylenes (pK_a (H₂O) = 11–13), such as malonitrile, bis(phenylsulfonyl) methane or methyl (phenylsulfonyl)acetate, were tested and showed no reactivity or led to intractable mixtures (See SI).

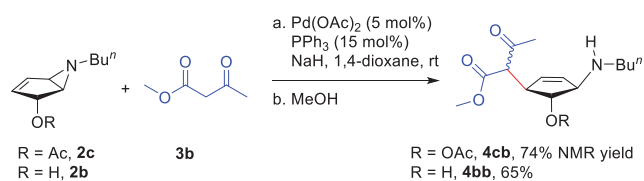
2.3. Structural assignment of the allylation products

In all the cases studied, product NMR analysis allowed to unambiguously establish that the reaction gave rise to a single product, constantly resulting from attack of the carbon nucleophile

Table 2
Substrate scope of the Pd(0)-catalyzed allylic substitution under base-free conditions.^a



^a Isolated yields. ^b Isolated product with traces of triphenylphosphine oxide (in parenthesis, NMR yield using 1,4-dinitrobenzene as internal standard)



Scheme 6. Pd(0)-catalyzed allylic substitution in the presence of base with methyl acetoacetate **3b**.

to the olefinic C3 carbon atom vicinal to the oxy function with vinylogous aziridine opening. The single-crystal X-ray structural analysis of the adduct **4ce** confirmed the above structural assignment and unveiled the relative *trans* stereochemistry around the three contiguous stereogenic centers of the cyclopentene structure [39].

Analogies among all the ¹H and ¹³C NMR spectra of the allylation products allowed to tentatively assign the same *trans* relative configuration to all the other obtained products. Furthermore, this X-ray structure reveals that **4ce** exists as an inner salt (Fig. 1). This feature is in line with the high polarity observed for this product and the other products of allylic substitution derived from the most acidic active methylenes. However, the equilibrium between the non-ionic and the inner salt forms in the allylic substitution

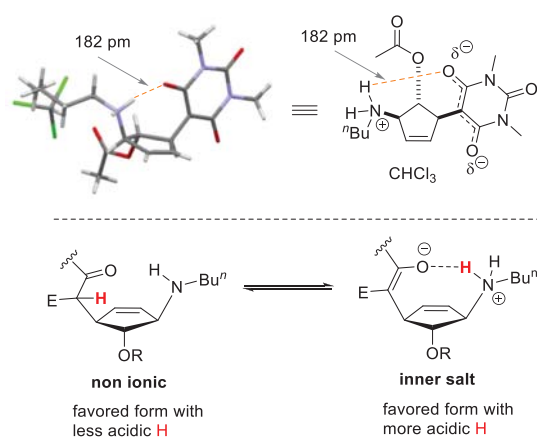


Fig. 1. Top: Single-crystal X-ray structural analysis of the adduct **4ce**. Indicated distance between an oxygen atom of the *N*-dimethyl barbituric fragment and a calculated H atom on the N atom. Bottom: equilibrium between the non-ionic and the inner salt forms of the allylic substitution product, whose position depends on the acidity of the proton left on the active methylene moiety after the substitution.

products depends on the degree of acidity of the proton left on the active methylene moiety after the substitution, and only those

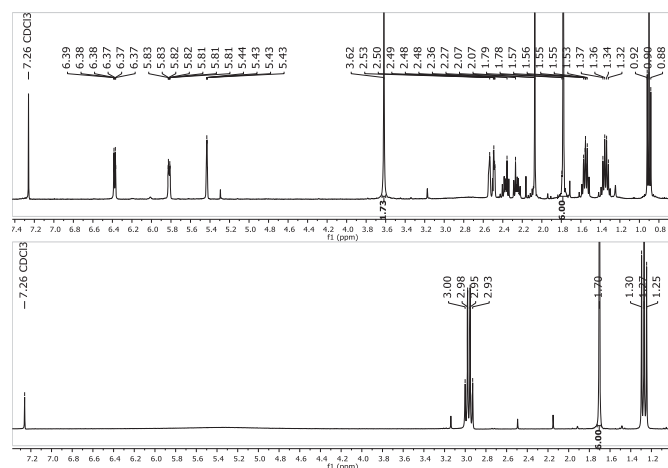


Fig. 2. Top: ^1H NMR spectrum of an equimolar mixture of the couple [Meldrum's acid **3c**/aziridine **2b**]; bottom: ^1H NMR spectrum of an equimolar mixture of the couple [Meldrum's acid **3c**/ NEt_3].

deriving from the most acidic pro-nucleophiles are found as inner salts [40].

2.4. Proposal of the mechanism

To gain insight into the chronology of the proton transfers involved in the transformation under study, we ran ^1H NMR spectra of equimolar mixtures of the couples [Meldrum's acid **3c**/aziridine **2b**] and [Meldrum's acid **3c**/ NEt_3] in CDCl_3 (Fig. 2). Interestingly, while the spectrum of the couple [Meldrum's acid **3c**/aziridine **2b**] showed no significant deviation with respect to the simple superposition of the spectra of the two single components, the one of [Meldrum's acid **3c**/ NEt_3] showed the absence of the methylene peak of Meldrum's acid (Fig. 2). The above result unequivocally shows that, in contrast to the behavior of a classical amine such as NEt_3 , aziridine **2b** is not capable of deprotonating to an apparent extent the active methylene. This result, which is in line with the known weak basicity of the aziridine nitrogen atom [41–43], indicates that in our reaction deprotonation of the active methylene has to take place only after aziridine opening (Scheme 7).

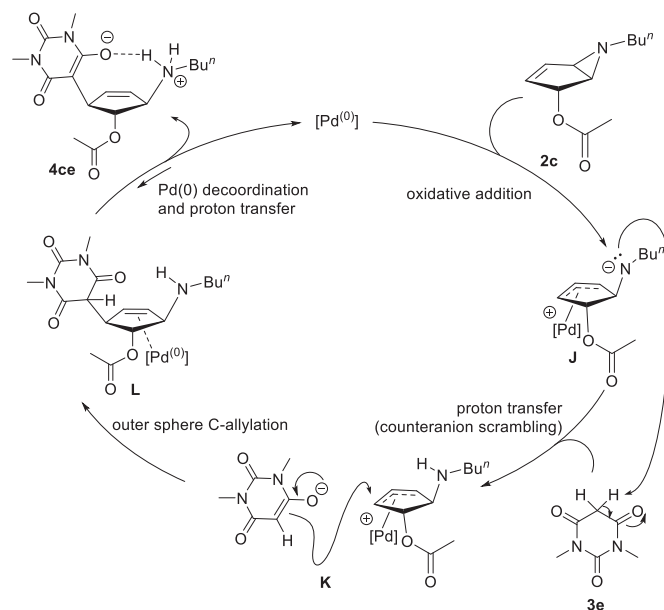
A plausible mechanism for this annulation, exemplified for the reaction between *N,N*-dimethyl barbituric acid **3e** and aziridine **2c**, is presented in Scheme 7.

Coordination of the $\text{Pd}(0)$ complex by the alkene function of the substrate from the face *syn* to the acetate group triggers aziridine opening with concomitant formation of the zwitterionic η^3 -allyl-palladium complex **J** (Scheme 7). Following proton transfer between **J** and the active methylene generates intermediate **K**, ready for an outer sphere C-allylation to afford intermediate **L**. Finally, $\text{Pd}(0)$ decoordination and proton transfer generates the final allylation product **4ce** and regenerates the $\text{Pd}(0)$ active catalyst.

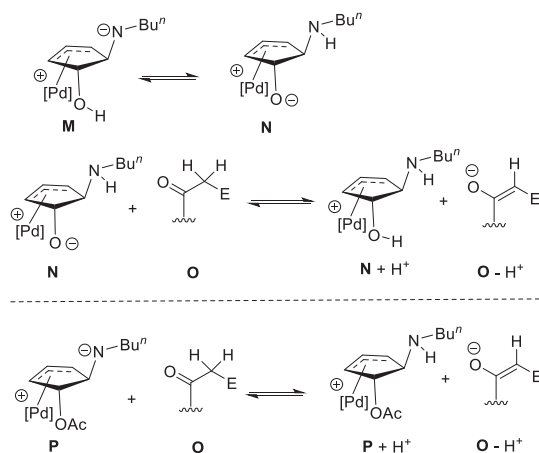
A little variant of the above mechanism has to be taken into account when the cyclopenten-aziridines carrying the free alcohol are used (Scheme 8). In this case, after the oxidative addition, intramolecular proton transfer from the alcohol function to amide anion ($\text{M} \rightleftharpoons \text{N}$) competes with the direct deprotonation of the active methylene [$\text{P} + \text{O} \rightleftharpoons (\text{P} + \text{H}^+) + (\text{O}-\text{H}^+)$] (Scheme 8).

3. Conclusion

In conclusion, in this study we have developed the first Pd -catalyzed allylic substitution between 2-oxy-cyclopenten-aziridines and active methylenes. In all the cases studied, the C-



Scheme 7. Proposed mechanism for the $\text{Pd}(0)$ -catalyzed allylic substitution of aziridine **2c**.



Scheme 8. Proton transfer equilibria after the oxidative addition step. Top: when using an hydroxycyclopenten-aziridine. Bottom: when using an acetoxycyclopenten-aziridine.

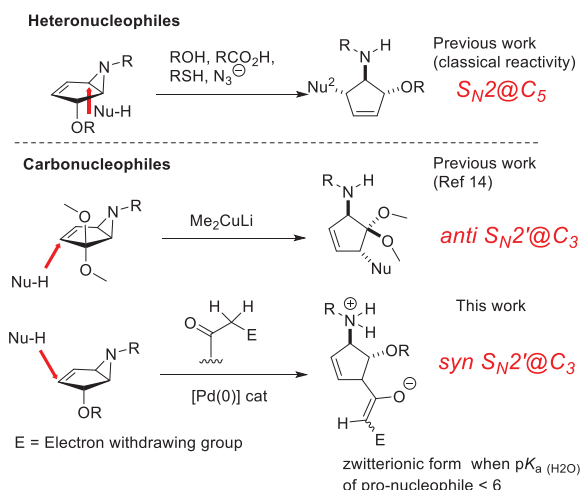
nucleophile substituted the position C3 of the cyclopentene moiety, *anti* to the allylic oxy group, with vinylogous ring opening of the aziridine ring, according to a *syn* $\text{S}_{\text{N}}2'$ mode. This new selectivity paradigm adds to the already known ones, enriching the chemistry of the 2-oxy-cyclopenten-aziridines. Interestingly, the equilibrium between the non-ionic and the inner salt forms in the allylic substitution products depends on the acidity of the proton left on the active methylene moiety after the substitution (Scheme 9).

4. Experimental section

4.1. General considerations

All reactions were carried out under an argon atmosphere by standard syringe and septa techniques. Et_2O was dried on a MBraun purification system MB SPS-800. 1,4-Dioxane was distilled from Na /benzophenone keep under N_2 atmosphere.

NMR spectra (^1H , ^{13}C) were recorded on a Bruker Fourier 300 or Bruker AM 300 MHz or Bruker AVANCE 400 MHz spectrometer.



Scheme 9. Reactivity modes in the allylic substitution of 2-oxy cyclopenten-aziridines.

NMR experiments were carried out at room temperature in CDCl₃ or D₂O. Chemical shifts are given in parts per million (ppm). The proton signal of residual non-deuterated solvent (δ 7.26 ppm for CHCl₃) was used as an internal reference for ¹H spectra. The carbon signal of deuterated solvent (δ 77.16 ppm for CDCl₃) was used as an internal reference for ¹³C spectra. Coupling constants (*J*) are given in Hertz (Hz). For previously unknown compounds, a combination of 2D experiments (HSQC, COSY and HMBC) were often used to complete assignment of ¹H and ¹³C signals. IR spectra were recorded with a Tensor 27 (ATR Diamond) Bruker spectrophotometer. IR spectra were reported as characteristic bands (cm⁻¹). High-resolution mass spectra (HRMS) were recorded using a mass spectrometer MicroTOF from Bruker with an electron spray ion source (ESI) and a TOF detector or using a mass spectrometer from Thermo Fisher Scientific with an electron spray ion source (ESI) and a LTQ Orbitrap as detector at Institut Parisien de Chimie Moléculaire. Melting points were measured in capillary tubes on a Stuart Scientific SMP3 apparatus and are uncorrected.

4.2. General base-free procedure in Et₂O

In a Schlenk equipped with a stir bar and purged under an argon atmosphere, was prepared a solution of palladium acetate (5 mol%) and triphenylphosphine (15 mol%) in distilled diethyl ether (0.5 mL). The solution was let stirring for 10 min at room temperature. Then, a solution of aziridine (50 mg, 1.0 equiv) in distilled diethyl ether (0.5 mL) was added and let stirring for another 10 min. The nucleophile (1.2 equiv) was added and the mixture was stirred at room temperature (25 °C). The reaction mixture was dissolved in methanol, and the solvent was removed under reduced pressure. The reaction crude was analyzed by ¹H NMR and the crude product was purified by silica gel chromatography.

4.2.1. 5-((1*R**,4*R**,5*R**)-5-acetoxy-4-(butylammonio)cyclopent-2-en-1-yl)-2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-olate **4 cc**

From aziridine **2c** (50 mg, 0.26 mmol, 1 equiv) and Meldrum's acid (44 mg, 0.31 mmol, 1.2 equiv). The mixture was stirred at room temperature for 5 h. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane/acetone (60/40) to afford 61 mg of **4 cc** (71% yield) as a brown solid. **m.p.** 137.0–137.2 °C. **¹H NMR** (400 MHz, CDCl₃) δ 9.87 (s, 1H), 9.55 (s, 1H), 5.98 (dd, *J* = 5.7, 2.7 Hz, 1H), 5.73 (dd, *J* = 5.5, 2.6 Hz, 1H), 5.28 (s, 1H), 3.97 (t, *J* = 2.5 Hz, 1H), 3.75 (s, 1H), 3.28 (d, *J* = 9.7 Hz, 1H), 2.94 (s, 1H), 2.05 (s, 3H), 1.69 (p, *J* = 7.6 Hz, 2H), 1.59 (s, 6H),

1.42–1.36 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.7, 167.3, 141.8, 122.1, 102.0, 79.4, 74.0, 69.8, 48.3, 46.0, 28.8, 25.7, 21.3, 20.0, 13.7. **IR** (cm⁻¹): 3427, 2962, 2935, 2870, 2459, 2250, 2184, 2139, 2057, 2031, 2013, 1970, 1933, 1737, 1653, 1548, 1460, 1399, 1369, 1235, 1202, 1165, 1133, 1103, 1049, 1023, 993, 911, 805, 777, 744, 644, 604, 578, 520, 422, 396. **HRMS (ESI)** calcd for C₁₇H₂₆NO₆ [M+H]⁺: 340.1755; found: 340.1756.

4.2.2. 5-((1*R**,4*R**,5*R**)-4-(butylammonio)-5-hydroxycyclopent-2-en-1-yl)-2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-olate **4bc**

From aziridine **2b** (50 mg, 0.32 mmol, 1 equiv) and Meldrum's acid (56 mg, 0.39 mmol, 1.2 equiv). The mixture was stirred at room temperature for 22 h. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane/acetone (20/80) to afford 42 mg of **4bc** (44% yield) as a brown solid. **m.p.** 155.2–155.4 °C. **¹H NMR** (400 MHz, CDCl₃) δ 9.71 (s, 1H), 9.15 (s, 1H), 6.03 (dd, *J* = 5.8, 2.7 Hz, 1H), 5.70–5.67 (m, 1H), 4.20 (s, 1H), 3.82 (s, 1H), 3.77 (t, *J* = 2.5 Hz, 1H), 2.94–2.91 (m, 2H), 1.72–1.63 (m, 2H), 1.59 (s, 6H), 1.39 (h, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 167.8, 143.3, 121.0, 102.1, 80.0, 74.8, 70.8, 51.0, 44.9, 28.9, 25.7, 25.6, 20.0, 13.71. **IR** (cm⁻¹): 2965, 2184, 2139, 2047, 2030, 2007, 1541, 1460, 1400, 1371, 1259, 1203, 1164, 1134, 1105, 1061, 998, 914, 816, 778, 730, 645, 586, 522, 425, 391. **HRMS (ESI)** calcd for C₁₅H₂₄NO₅ [M+H]⁺: 298.1649; found: 298.1650.

4.2.3. 5-((4*R**,5*R**)-5-acetoxy-4-((3-acetoxypropyl)ammonio)cyclopent-2-en-1-yl)-2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-olate **4dc**

From aziridine **2d** (51.1 mg, 0.21 mmol) and Meldrum's acid (36.2 mg, 0.25 mmol). The mixture was stirred at room temperature for 3 h. The reaction crude product was purified by flash chromatography on silica gel eluting with dichloromethane/acetone (80/20; 60/40) to afford 41.4 mg of **4dc** as an orange oil (52%). **¹H NMR** (300 MHz, CDCl₃) δ 10.20 (s, 1H), 9.63 (s, 1H), 6.06 (dd, *J* = 5.6, 2.7 Hz, 1H), 5.74 (s, 1H), 5.26 (s, 1H), 4.20–4.12 (m, 2H), 4.02 (m, 1H), 3.79 (s, 1H), 3.41 (s, 1H), 3.09 (s, 1H), 2.12–2.04 (m, 8H), 1.62 (s, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ 171.4, 171.1, 167.3, 142.6, 121.6, 102.2, 79.5, 77.6, 74.1, 69.6, 61.3, 47.9, 43.2, 29.8, 26.2, 25.7, 21.3, 21.0. **IR** (cm⁻¹): 2927, 1727, 1556, 1455, 1404, 1371, 1245, 1166, 1101, 1018, 874, 808, 779, 727, 521. **HRMS *m/z*** calcd for C₁₈H₂₆NO₈ [M+H]⁺: 384.1653; found 384.1650.

4.2.4. (1*R**,2*R**)-2-(butylamino)-5-(2,2,5-trimethyl-4,6-dioxo-1,3-dioxan-5-yl)cyclopent-3-en-1-yl acetate **4cd**

From palladium acetate (3.0 mg, 10 mol%) and triphenylphosphine (10.1 mg, 30 mol%), aziridine **2c** (25.5 mg, 1.0 equiv) and methylated Meldrum's acid **3d** (24.4 mg, 1.2 equiv). The mixture was stirred at room temperature for 5 h. The reaction mixture was dissolved in methanol, and the solvent was removed under reduced pressure. The reaction crude was purified by flash column chromatography dichloromethane/methanol (99/1; 98/2) to afford the product **4cd** as a yellow oil (11.8 mg, 26%). This product was isolated with trace amounts of triphenylphosphine oxide (around 20%), NMR yield of 65%. **¹H NMR** (400 MHz, CDCl₃) δ 5.91–5.89 (m, 1H), 5.67 (d, *J* = 6.1 Hz, 1H), 5.53 (dd, *J* = 4.0, 3.1 Hz, 1H), 3.71 (dd, *J* = 4.5, 2.5 Hz, 1H), 3.37–3.36 (m, 1H), 2.70–2.57 (m, 2H), 2.07 (s, 3H), 1.76 (s, 3H), 1.72 (s, 3H), 1.68 (s, 3H), 1.45–1.32 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.3, 169.5, 135.3, 127.8, 105.4, 78.2, 71.1, 60.9, 51.5, 46.8, 32.5, 30.3, 28.2, 21.3, 21.2, 20.5, 14.1. **IR** (cm⁻¹): 2973, 1740, 1618, 1233, 1046, 880, 723, 542. **HRMS *m/z*** calcd for C₁₈H₂₈NO₆ [M+H]⁺: 354.1911; found 354.1912.

4.2.5. 5-((1*R**,4*R**,5*R**)-5-acetoxy-4-(butylammonio)cyclopent-2-en-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate **4ce**

From aziridine **2c** (50 mg, 0.26 mmol, 1 equiv) and 1,3-dimethylbarbituric acid **3e** (48 mg, 0.31 mmol, 1.2 equiv). The mixture was stirred at room temperature for 18 h. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane/acetone (40/60; 30/70; 20/80) to afford 63 mg of **4ce** (83% yield) as a brown solid. **m.p.** 240–242 °C. ¹H NMR (300 MHz CDCl₃) δ 10.58 (s, 1H), 9.48 (s, 1H), 5.99 (dd, *J* = 5.7, 2.7 Hz, 1H), 5.63 (d, *J* = 5.7 Hz, 1H), 5.19 (s, 1H), 4.31 (s, 1H), 3.77 (s, 1H), 3.67 (s, 1H), 3.21 (s, 6H), 3.03 (s, 1H), 2.02 (s, 3H), 1.83–1.57 (m, 2H), 1.46 (ddd, *J* = 8.5, 7.3, 5.8 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 164.9, 153.0, 142.7, 121.5, 85.6, 80.1, 69.4, 48.0, 45.7, 39.5, 28.9, 28.6, 27.9, 21.2, 19.9, 13.7. IR (cm⁻¹): 2924, 2854, 1735, 1675, 1573, 1436, 1374, 1314, 1240, 1165, 1067, 1023, 776, 518, 483. HRMS (ESI) calcd for C₁₇H₂₆N₃O₅ [M+H]⁺: 352.1867; found: 352.1867.

4.2.6. 5-((1*R**,4*R**,5*R**)-4-(butylammonio)-5-hydroxycyclopent-2-en-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate **4be**

From aziridine **2c** (50 mg, 0.32 mmol, 1 equiv) and 1,3-dimethylbarbituric acid **3e** (61 mg, 0.39 mmol, 1.2 equiv). The mixture was stirred at room temperature for 18 h. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane/acetone (90/10); Acetone and acetone/methanol (95/5); to afford 38 mg of **4be** (42% yield) as a brown solid. **m.p.** 211–215 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.43 (s, 1H), 9.23 (s, 1H), 5.95 (dd, *J* = 5.7, 2.7 Hz, 1H), 5.68 (d, *J* = 5.7 Hz, 1H), 4.15 (s, 1H), 3.99 (t, *J* = 2.4 Hz, 1H), 3.85 (d, *J* = 2.1 Hz, 1H), 3.18 (s, 6H), 3.01–2.94 (m, 2H), 1.71 (q, *J* = 7.6 Hz, 2H), 1.43 (p, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 163.7, 152.7, 143.0, 121.1, 86.5, 79.5, 70.5, 51.5, 44.7, 28.9, 27.9, 19.9, 13.7. IR (cm⁻¹): 3350, 2958, 2925, 2854, 1661, 1565, 1430, 1373, 1311, 1262, 1241, 1065, 1014, 963, 888, 796, 774, 732, 701, 582, 517, 485, 419. HRMS (ESI) calcd for C₁₅H₂₄N₃O₄ [M+H]⁺: 310.1761; found: 310.1760.

4.2.7. Ethyl 2-((1*R**,4*R**,5*R**)-5-acetoxy-4-(butylamino)cyclopent-2-en-1-yl)-2-nitroacetate **4cf**

From aziridine **2c** (50 mg, 0.26 mmol, 1 equiv) and ethyl nitroacetate **3f** (40.9 mg, 0.31 mmol, 1.2 equiv). The mixture was stirred at room temperature for 5 h. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane/ethyl acetate (70/30) followed by crystallization with cold diethyl ether and filtration to afford 20 mg of **4cf** (24% yield) as a brown solid. This product was difficult to isolate pure due to the presence of triphenylphosphine oxide (71% NMR yield). **m.p.** 46–50 °C. **1/1 diastereoisomeric mixture** ¹H NMR (400 MHz, CDCl₃) δ 5.99–5.92 (m, 1H, dia A + B), 5.80 (d, *J* = 6.0 Hz, 1H, dia A), 5.76 (d, *J* = 6.1 Hz, 1H, dia B), 5.55 (d, *J* = 6.4 Hz, 1H, dia A + B), 5.12–5.07 (m, 1H, dia A), 5.05–5.01 (m, 1H, dia B), 4.35–4.24 (m, 2H, dia A + B), 3.79 (s, 1H, dia A + B), 3.48 (s, 1H, dia A), 3.43 (s, 1H, dia B), 2.69–2.57 (m, 2H, dia A + B), 2.13–2.95 (m, 3H, dia A + B), 1.50–1.40 (m, 2H, dia A + B), 1.39–1.27 (m, 5H, dia A + B), 0.91 (t, *J* = 7.2 Hz, 3H, dia A + B). ¹³C NMR (101 MHz, CDCl₃) δ 171.3, 171.1, 135.6, 135.3, 128.7, 128.2, 89.8, 88.9, 80.6, 80.6, 69.9, 69.8, 63.3, 63.3, 52.9, 52.8, 47.4, 47.3, 32.6, 32.5, 21.1, 21.1, 20.5, 14.1, 13.9. IR (cm⁻¹): 3287, 2920, 2852, 1640, 1547, 1313, 1255, 1204, 697. HRMS (ESI) calcd for C₁₅H₂₅N₂O₆ [M+H]⁺: 329.1707; obtained: 329.1706.

4.2.8. Ethyl 2-((1*R**,4*R**,5*R**)-4-(butylamino)-5-hydroxycyclopent-2-en-1-yl)-2-nitroacetate **4bf**

From aziridine **2b** (50 mg, 0.32 mmol, 1 equiv) and ethyl nitroacetate **3f** (52 mg, 0.39 mmol, 1.2 equiv). The mixture was stirred at

room temperature for 1 h. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane/ethyl acetate (1:1) and cyclohexane/ethyl acetate/methanol (49.8/49.8/0.2; 49.5/49.5/1) to afford 30 mg of **4bf** (32% yield) as a brown solid. **m.p.** 40–44 °C. **1/1 diastereoisomeric mixture** ¹H NMR (300 MHz, CDCl₃) δ 5.68 (d, *J* = 3.1 Hz, 1H, dia A), 5.58 (d, *J* = 3.0 Hz, 1H, dia B), 5.05 (d, *J* = 7.7 Hz, 1H, dia A), 4.96 (d, *J* = 8.7 Hz, 1H, dia B), 4.30 (p, *J* = 7.1 Hz, 2H, dia A + B), 4.02 (s, 1H, dia A + B), 3.80–3.73 (m, 1H, dia A + B), 3.00–2.93 (m, 2H, dia A + B), 2.78–2.66 (m, 1H, dia A + B), 2.47–2.34 (m, 1H, dia A + B), 1.52 (p, *J* = 7.1 Hz, 2H, dia A + B), 1.41–1.32 (m, 2H, dia A + B), 1.30 (td, *J* = 7.1, 2.5 Hz, 3H, dia A + B), 0.92 (t, *J* = 7.3 Hz, 3H, dia A + B). ¹³C NMR (101 MHz, CDCl₃) δ 200.8, 200.7, 163.3, 163.2, 147.7, 147.7, 114.1, 113.5, 91.4, 90.8, 77.3, 77.0, 76.7, 63.2, 63.2, 43.8, 37.6, 37.2, 37.1, 36.7, 30.9, 20.1, 13.9, 13.9, 13.7. IR (cm⁻¹): 3287, 2918, 1640, 1544, 1314, 1255, 1204, 1143, 890, 676. HRMS (ESI) calcd for C₁₃H₂₃N₂O₅ [M+H]⁺: 287.1601; found: 287.1603.

4.3. General procedure with NaH in 1,4-dioxane

In a Schlenk tube under an argon was prepared a solution of Pd(OAc)₂ (5 mol%) and PPh₃ (15 mol%) in 0.5 mL of distilled 1,4-dioxane. After 10 min of stirring, the aziridine (50 mg, 1 equiv) dissolved in 0.5 mL of distilled 1,4-dioxane was added, and the mixture was stirred for another 10 min. A solution of the nucleophile (1.2 equiv) deprotonated by sodium hydride (1.2 equiv) in 0.5 mL of 1,4-dioxane was added to the previous mixture. The mixture was stirred at room temperature (25 °C) overnight (18 h), and then dissolved with methanol. The solvent was evaporated, and the crude product was purified by column chromatographic to afford the desired product.

4.3.1. Methyl 2-((1*R**,4*R**,5*R**)-5-acetoxy-4-(butylamino)cyclopent-2-en-1-yl)-3-oxobutanoate **4cb**

From aziridine **2c** (50.5 mg, 0.26 mmol, 1 equiv) and methyl acetoacetate (35.7 mg, 0.39 mmol, 1.2 equiv). The purification of the crude product (NMR 74% using 1,4-nitroacetate as internal standard) on silica gel eluting with cyclohexane/ethylacetate (60/40; 30/70) did not allow to isolate pure the product **4cb** without triphenylphosphine oxide contamination. **1/1 diastereoisomeric mixture** ¹H NMR (400 MHz, CDCl₃) δ 5.81 (dq, *J* = 4.9, 2.3 Hz, 1H, dia A + B), 5.71 (ddd, *J* = 5.5, 3.4, 1.7 Hz, 1H, dia A + B), 4.97 (t, *J* = 4 Hz, 1H, dia A), 4.89 (t, *J* = 4 Hz, 1H, dia B), 3.88 (s, 1H, dia A), 3.86 (s, 1H, dia B), 3.74 (s, 3H, dia A), 3.72 (s, 3H, dia B), 3.30–3.27 (m, 1H, dia A + B), 2.66–2.60 (m, 1H, dia A + B), 2.25 (s, 3H, dia A), 2.24 (s, 3H, dia B), 2.06 (s, 3H, dia A), 2.05 (s, 3H, dia B), 1.49–1.24 (m, 4H, dia A + B), 0.91 (t, *J* = 7.2 Hz, 3H, dia A + B). ¹³C NMR (75 MHz, CDCl₃) δ 202.0, 201.7, 171.2, 170.9, 169.0, 133.4, 133.0, 132.9, 132.0, 132.0, 131.5, 131.5, 82.3, 81.6, 70.2, 69.9, 62.5, 52.7, 52.5, 50.7, 50.3, 47.3, 47.2, 32.6, 32.6, 30.4, 29.9, 21.2, 20.5, 20.5, 14.1. IR (cm⁻¹): 2954, 2925, 1742, 1676, 1536, 1424, 1377, 1323, 1241, 1197, 1166, 1140, 1107, 1037, 785, 767, 750. HRMS (ESI) calcd for C₁₆H₂₆NO₅ [M+H]⁺: 312.1805; found: 312.1802.

4.3.2. Methyl 2-((1*R**,4*R**,5*R**)-4-(butylamino)-5-hydroxycyclopent-2-en-1-yl)-3-oxobutanoate **4bb**

From aziridine **2b** (50 mg, 0.32 mmol, 1 equiv) and acetoacetate (45 mg, 0.39 mmol, 1.2 equiv). The crude product was purified by flash chromatography on silica gel eluting with dichloromethane/acetone (40/60) to afford 57 mg of **4bb** (65% yield) as a brown oil. **1/1 diastereoisomeric mixture** ¹H NMR (400 MHz, CDCl₃) δ 5.80 (dt, *J* = 6.2, 2.1 Hz, 1H, dia A + B), 5.66 (dt, *J* = 6.1, 1.8 Hz, 1H, dia A), 5.58 (dt, *J* = 6.1, 1.9 Hz, 1H, dia B), 4.05 (t, *J* = 5.1 Hz, 1H, dia A), 3.95 (t, *J* = 5.2 Hz, 1H, dia B), 3.82–3.75 (m, 1H, dia A + B), 3.75 (s, 3H, dia A), 3.74 (s, 3H, dia B), 3.68 (d, *J* = 8.9 Hz, 1H, dia A), 3.65 (d,

$J = 9.1$ Hz, 1H, dia B), 3.23–3.14 (m, 1H, dia A + B), 2.78–2.72 (m, 2H, dia A + B), 2.27 (s, 3H, dia A + B), 1.62–1.47 (m, 2H, dia A + B), 1.43–1.27 (m, 2H, dia A + B), 0.91 (t, $J = 7.4$ Hz, 3H, dia A + B). ^{13}C NMR (101 MHz, CDCl_3) δ 203.6, 202.7, 170.0, 169.3, 132.4, 131.6, 131.4, 130.7, 81.5 (2C), 71.4, 63.1, 62.4, 52.9, 52.8, 52.1, 51.8, 47.0, 31.7, 31.4, 30.3, 29.7, 20.5, 14.0, 14.0. IR (cm^{-1}): 3348, 2956, 2930, 2872, 2126, 2006, 1978, 1713, 1647, 1577, 1529, 1460, 1424, 1375, 1327, 1253, 1212, 1185, 1163, 1106, 1055, 1029, 978, 939, 898, 860, 789, 765, 751, 683, 613, 533, 473, 392. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{24}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 270.1700; found: 270.1700.

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- [36] For a chapter review, see: C. Kammerer-Pentier, F. Liron, G. Prestat, G. Poli, *Selectivity in palladium catalyzed allylic substitution*, in: U. Kazmaier (Ed.), *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, vol. 38, *Topics in Organometallic Chemistry*; Springer-Verlag, Berlin Heidelberg, 2012, pp. 1–64.
- [37] See Supporting Information for Detailed Optimization.
- [38] We were not able to totally remove traces of triphenylphosphine oxide from the isolated compound **4cb**.
- [39] Crystallographic data was deposited at the Cambridge Crystallographic Data Centre with number CCDC 1980421.
- [40] The ratio of neutral to zwitterionic form is expected to be rather context dependent and may be different in going from solid state to solution, or in solvents with differing dielectric constants. We thank a referee for this remark.
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