Journal Pre-proof

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

João A.C. Oliveira, Gredy Kiala, Filipa Siopa, Aurélie Bernard, Geoffrey Gontard, Julie Oble, CarlosA.M. Afonso, Giovanni Poli

PII: S0040-4020(20)30317-3

DOI: https://doi.org/10.1016/j.tet.2020.131182

Reference: TET 131182

To appear in: *Tetrahedron*

Received Date: 8 February 2020

Revised Date: 31 March 2020

Accepted Date: 3 April 2020

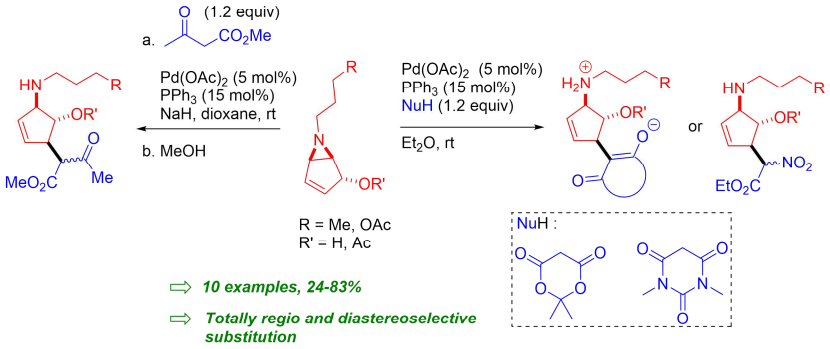
Please cite this article as: Oliveira JoãAC, Kiala G, Siopa F, Bernard Auré, Gontard G, Oble J, Afonso CM, Poli G, Palladium-catalyzed allylic substitution between C-based nucleophiles and 6-azabicyclo[3.1.0]-hex-3-en-2-oxy derivatives: A new selectivity paradigm, *Tetrahedron* (2020), doi: https://doi.org/10.1016/j.tet.2020.131182.

.

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

Leave this area blank for abstract info.

João A. C. Oliveira, Gredy Kiala, Filipa Siopa,* Aurélie Bernard, Geoffrey Gontard, Julie Oble,* Carlos A. M. Afonso* and Giovanni Poli*



Tetrahedron
journal homepage: www.elsevier.com

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

João A. C. Oliveira,[a,b] Gredy Kiala,[a,b] Filipa Siopa,[a,b]* Aurélie Bernard,[a] Geoffrey Gontard,[a] Julie Oble,[a]* Carlos A. M. Afonso[b]* and Giovanni Poli[a]*

[a] *Sorbonne Université, Faculté des Sciences et Ingénierie, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, 4 place Jussieu, 75005 Paris, France*
[b] *Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Palladium catalysis
Bicyclic aziridine
Tsuji-Trost reaction

ABSTRACT

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 ($pK_{a\ (DMSO)} \leq 7.3$), 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.

* Corresponding authors.

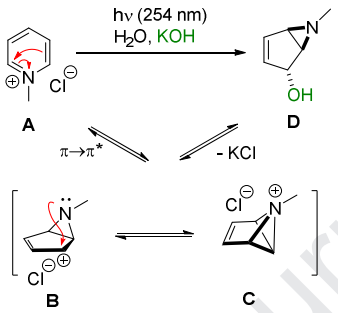
E-mail address: filipasiopa@ff.ulisboa.pt; julie.oble@sorbonne-universite.fr; carlosafonso@ff.ulisboa.pt; giovanni.poli@sorbonne-universite.fr.

1. Introduction

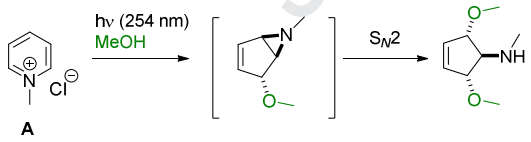
Aziridines are the smallest members of the aza-heterocycle family [1,2]. Due to their considerable ring strain, these molecules show in general a high reactivity that makes them major intermediates for organic synthesis. Furthermore, several biologically active natural products [3], or analogs of them,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

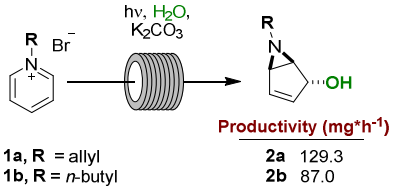


Scheme 1. Kaplan's pioneering studies: photochemical conversion of 1-methylpyridin-1-ium chloride **A** into α-hydroxycyclopenten-aziridine **D**[4].



Scheme 2. Photochemical electrocyclization of *N*-methyl-pyridinium chloride followed by methanolytic α-oxycyclopenten-aziridine opening [5].

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], [23-28]. 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 [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 $mg{\cdot}h^{-1}$ *vs* 39.4 $mg{\cdot}h^{-1}$) and 18:1 for **2b** [29] (87.0 $mg{\cdot}h^{-1}$ *vs* 4.8 $mg{\cdot}h^{-1}$) (Scheme 3).

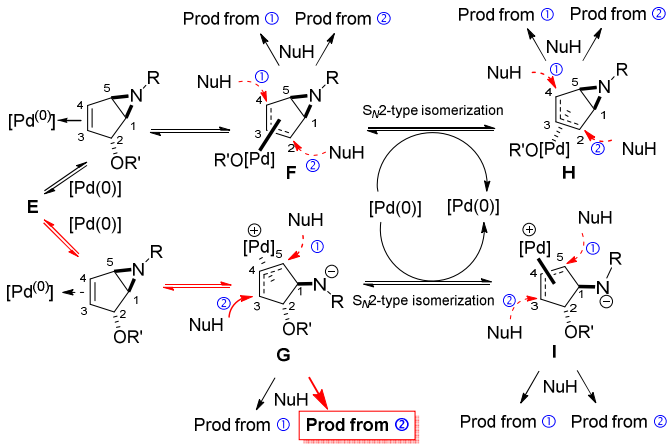


Scheme 3. Process intensification for the synthesis of α-hydroxycyclopenten-aziridines using continuous UV-light photoflow home-made reactors [29, 31].

Considering the peculiar structure of the above described α-oxycyclopenten-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-oxycyclopenten-aziridines.

Some preliminary considerations are worthy, before presenting the results. The cyclopentene motif in these α-oxycyclopenten-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 [36] may allow generation of intermediates **H** and/or **I** prior of the nucleophilic trapping. Finally, each of the four η^3-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.

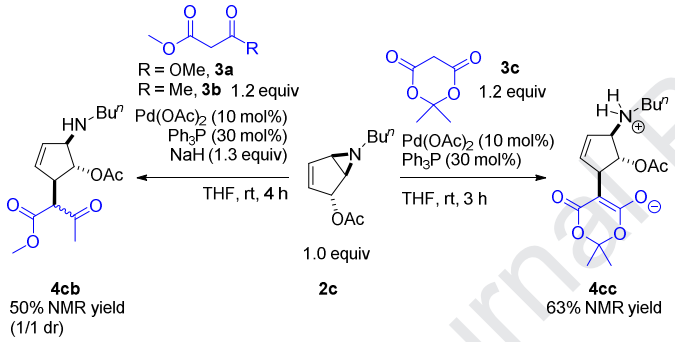


Scheme 4. Potential regio- and stereo-selectivities in the Pd(0)-catalyzed allylic substitution between α-oxycyclopenten-aziridines and carbon-based soft nucleophiles. In red the experimentally observed reactivity from **G**. Brackets around palladium atom in a charged or neutral complex intend to render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

2. Results/Discussion

2.1. Optimization of the reaction conditions

Dimethyl malonate **3a** ($pK_{a\ (H2O)}$ = 13; $pK_{a\ (DMSO)}$ = 15.9), methyl acetoacetate **3b** ($pK_{a\ (H2O)}$ = 11) and Meldrum's acid **3c** ($pK_{a\ (H2O)}$ = 5; $pK_{a\ (DMSO)}$ = 7.3) were first considered as C-based pro-nucleophiles for the reaction with α-acetoxycyclopenten-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 appropriate pK_a window to allow the allylic substitution to take place (Scheme 5).



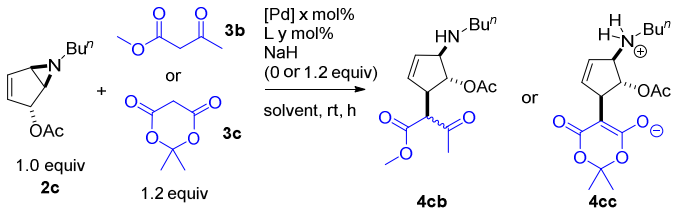
Scheme 5. Preliminary allylic substitution tests between methyl acetoacetate **3b** or Meldrum's acid **3c** and α-acetoxycyclopenten-aziridine **2c**.

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-acetoxycyclopenten-aziridine **2c** in presence of NaH, the use of phosphines other than PPh_3 (mono- or bidentate) did not allow further improvements (Table 1, entries 1-4). Switch to {[$Pd(\eta^3$-$C_3H_5)Cl]_2$ (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 Et_2O 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%) / PPh_3 (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 Et_2O 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%) / PPh_3 (15 mol%)] recording even a slight yield increase (Table 1, entry 12).

Table 1. Optimization of the reaction between methyl acetoacetate **3b** or Meldrum's acid **3c** with α-acetoxycyclopenten-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**	$[Pd(C_3H_5)Cl]_2$ (10)	dppe (20)	THF (18)	**4cb**, 8
6	**3b**	$Pd(OAc)_2$ (10)	PPh_3 (30)	Et_2O (4)	**4cb**, 59
7	**3b**	$Pd(OAc)_2$ (10)	PPh_3 (30)	DIOX (4)	**4cb**, 72
8	**3b**	**$Pd(OAc)_2$ (5)**	**PPh_3 (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_2O (3.5)	**4cc**, 84
12	**3c**	**$Pd(OAc)_2$ (5)**	**PPh_3 (15)**	**Et_2O (5)**	**4cc, 88**

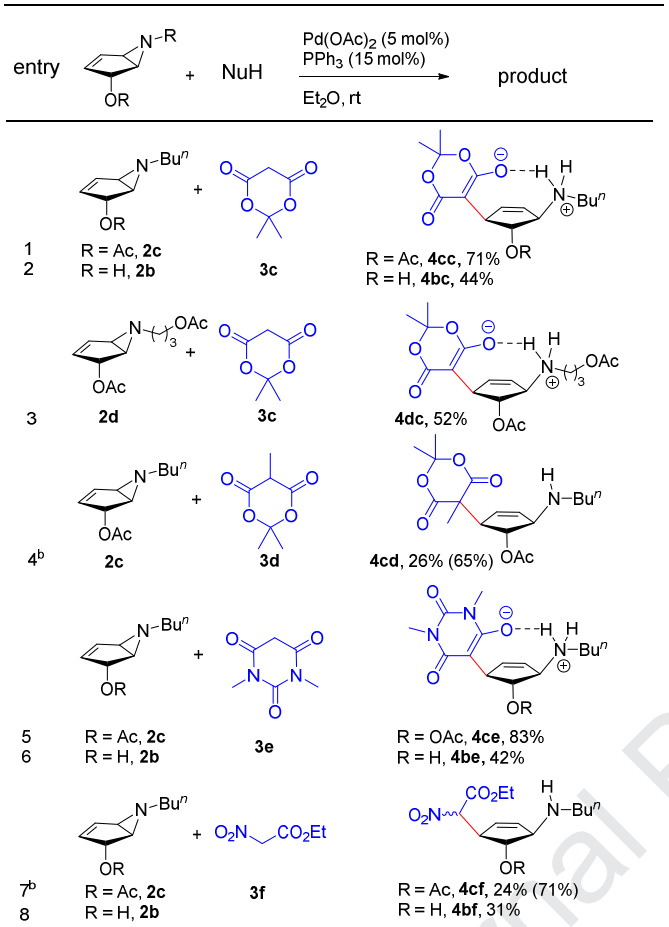
[a] Reaction conditions: **2c** (1.0 equiv), **3b** or **3c** (1.2 equiv), solvent (0.5 M), NaH (1.2 equiv: entry 1 to 8, or 0 equiv: entry 9 to 12). [b] Determined by ^{1}H NMR analysis of the crude product using 1,4-dinitrobenzene as internal standard. DIOX: 1-4-dioxane; Dppe: 1,2-bis(diphenylphosphino)ethane; dppf: 1,1′-ferrocenediyl-bis(diphenylphosphine), MeDCHB: 2-dicyclohexylphosphino-2′-methylbiphenyl.

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-acetoxycyclopenten-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-acetoxycyclopenten-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-acetoxycyclopenten-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

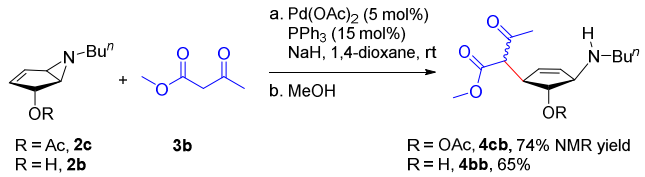
very acidic methylene ($pK_{a\ (H2O)}$ = 5.2; $pK_{a\ (DMSO)}$ = 11.2) was tested, but unfortunately led to an unanalyzable complex mixture.

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)

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, disulfone or methyl (phenylsulfonyl)acetate, were tested and showed no reactivity or led to intractable mixtures (See SI).



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

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 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 ^{1}H and ^{13}C 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, (Figure 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 products depends on the degree of acidity of the proton left on the active methylene moiety after the substitution, and only those deriving from the most acidic pro-nucleophiles are found as inner salts [40].

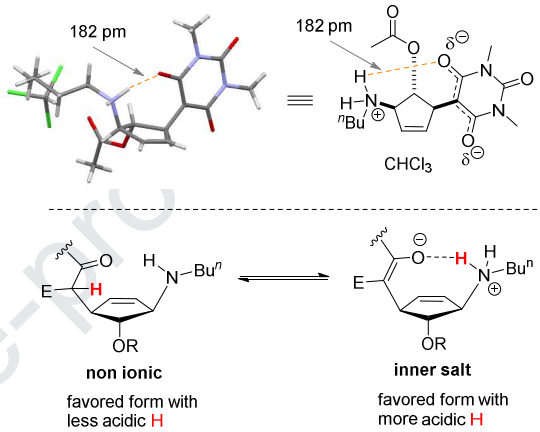


Figure 1. Top: Single-crystal X-ray structural analysis of the adduct **4ce**. Indicated distance between an oxygen atom of the *N*-dimethyl barbituric fragment and a calculated H atom on the N atom. Bottom: equilibrium between the non-ionic and the inner salt forms of the allylic substitution product,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

2.4. Proposal of the mechanism

To gain insight into the chronology of the proton transfers involved in the transformation under study, we ran ^{1}H NMR spectra of equimolar mixtures of the couples [Meldrum's acid **3c** / aziridine **2b**] and [Meldrum's acid **3c** / NEt_3] in $CDCl_3$ (Figure 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 (Figure 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).

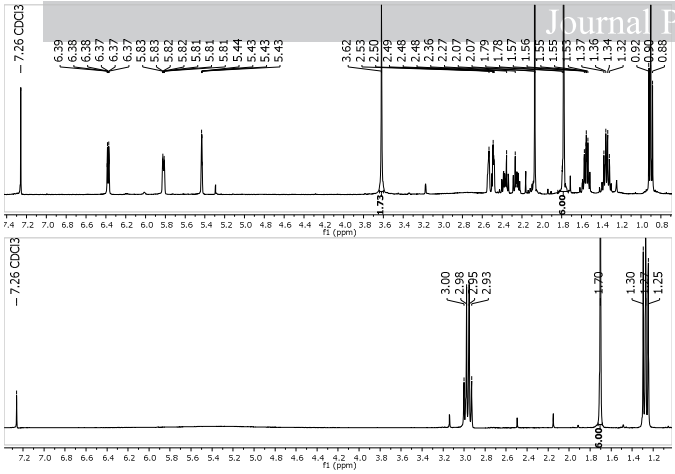
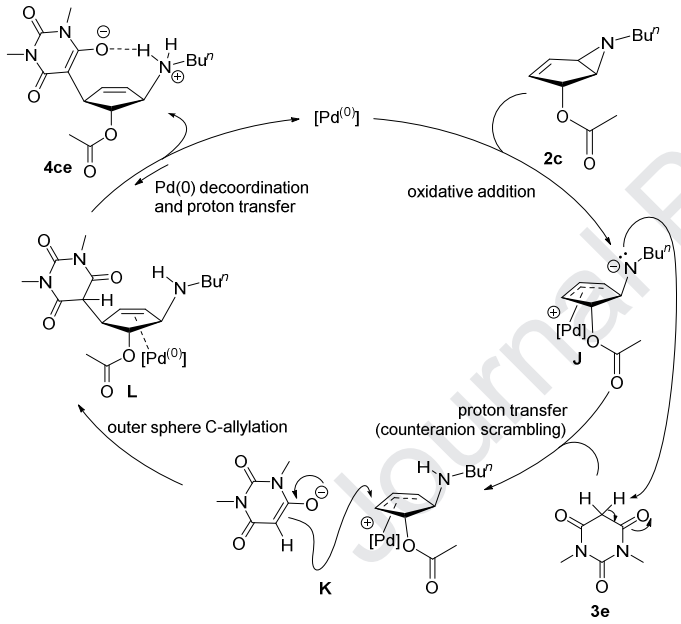


Figure 2. Top: ^{1}H NMR spectrum of an equimolar mixture of the couple [Meldrum's acid **3c** / aziridine **2b**]; bottom: ^{1}H NMR spectrum of an equimolar mixture of the couple [Meldrum's acid **3c** / NEt_3].

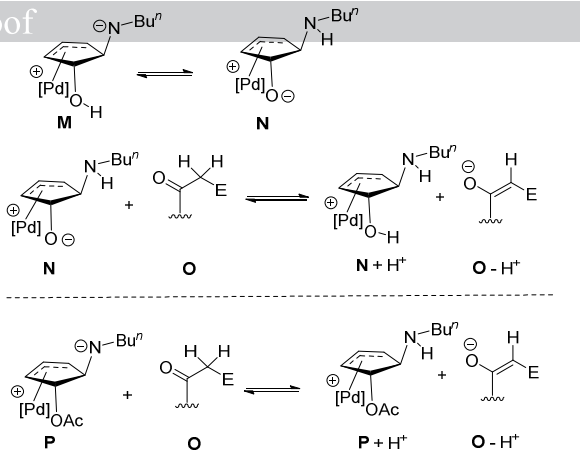
A plausible mechanism for this annulation, exemplified for the reaction between *N*,*N*-dimethyl barbituric acid **3e** and aziridine **2c**, is presented in Scheme 7.



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

Coordination of the 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-allylpalladium 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, Pd(0) decoordination and proton transfer generates the final allylation product **4ce** and regenerates the Pd(0) active catalyst.

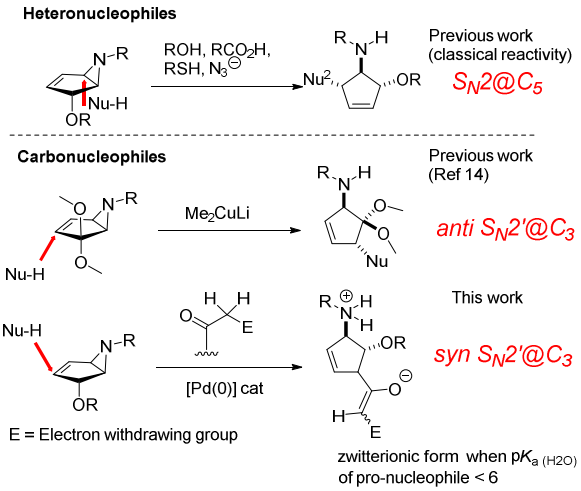
A little variant of the above mechanism has to be taken into account when the cyclopenten-aziridines carrying the free alcohol are used (Scheme 8). In this case, after the oxidative addition, intramolecular proton transfer from the alcohol function to amide anion (**M** ⇆ **N**) competes with the direct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



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

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-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* S_N2' 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).



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

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 (^{1}H, ^{13}C) were recorded on a Bruker Fourier 300 or Bruker AM 300 MHz or Bruker AVANCE 400 MHz spectrometer. NMR experiments were carried out at room temperature in $CDCl_3$ or D_2O. Chemical shifts are given in parts per million (ppm). The proton signal of residual non-deuterated

solvent (δ 7.26 ppm for $CHCl_3$) was used as an internal reference for ^1H spectra. The carbon signal of deuterated solvent (δ 77.16 ppm for $CDCl_3$) was used as an internal reference for ^{13}C 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 ^{13}C 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 Et_2O

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.

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

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 **4cc** (71% yield) as a brown solid. **m.p.** 137.0-137.2 °C.**^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) 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 $C_{17}H_{26}NO_6$ $[M+H]^+$: 340.1755; found: 340.1756.

5-((1*R,4*R**,5*R**)-4-(butylammonio)-5-hydroxycyclopent-2-en-1-yl)-2,2-dimethyl-4-oxo-4H-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.**^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) 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 $C_{15}H_{24}NO_5$ $[M+H]^+$: 298.1649; found: 298.1650.

5-((4*R,5*R**)-5-acetoxy-4-((3-acetoxypropyl)ammonio)cyclopent-2-en-1-yl)-2,2-dimethyl-4-oxo-4H-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 %). **^{1}H NMR** (300 MHz, $CDCl_3$) 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).**^{13}C NMR** (75 MHz, $CDCl_3$) 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 $C_{18}H_{26}NO_8$ $[M+H]^+$: 384.1653; found 384.1650.

(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 methyl meldrum 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%. **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) 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 $C_{18}H_{28}NO_6$ $[M+H]^+$: 354.1911; found 354.1912.

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. **^{1}H 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). **^{13}C NMR** (75 MHz, $CDCl_3$) 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 $C_{17}H_{26}N_3O_5$ $[M+H]^+$: 352.1867; found: 352.1867.

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. **^{1}H NMR** (400 MHz, $CDCl_3$) 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).**^{13}C NMR** (75 MHz, $CDCl_3$) 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 $C_{15}H_{24}N_3O_4$ $[M+H]^+$: 310.1761; found: 310.1760.

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 ^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) 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 $C_{15}H_{25}N_2O_6$ $[M+H]^+$: 329.1707; obtained: 329.1706.

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 ^{1}H NMR** (300 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) 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 $C_{13}H_{23}N_2O_5$ $[M+H]^+$: 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 PPh_3 (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 minutes. 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.

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 cyclohexene/ethylacetate (60/40; 30/70) did not allow to isolate pure the product **4cb** without triphenylphosphine oxide contamination. **1/1 diastereoisomeric mixture ^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (75 MHz, $CDCl_3$) 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 $C_{16}H_{26}NO_5$ $[M+H]^+$: 312.1805; found: 312.1802.

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 ^{1}H NMR** (400 MHz, $CDCl_3$) 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 $C_{14}H_{24}NO_4$ $[M+H]^+$: 270.1700; found: 270.1700.

Acknowledgments

The authors would like to acknowledge Horizon 2020 ERANet-LAC project CelluloseSynThech for financial support (ref. ELAC2014/BEE-0341), as well as CNRS, Sorbonne Université and Labex Michem (Investissements d'Avenir programme, ref. ANR-11-IDEX-0004-02), Fundação para a Ciência e Tecnologia (SFRH/BPD/88666/2012, PTDC/QUI-QOR/32008/2017, UID/DTP/04138/2019) and COMPETE Programme (SAICTPAC/0019/2015). Support through CMST COST Action, CA15106 (CHAOS) is also gratefully acknowledged.

Supplementary Material

Supplementary data to this article can be found online at https://doi.org/.

References and notes

[1] G. S. Singh, Heterocyclic Chem. 129 (2019) 245–335.
[2] M. C. McMills, S. C. Bergmeier, 1.02 - Aziridines and azirines: fused-ring derivatives. In Comprehensive Heterocyclic Chemistry III, A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Eds. Elsevier: Oxford, 2008; pp 105–172.
[3] S. Vandekerckhove, M. D'hooghe, Bioorg. Med. Chem. 21 (2013) 3643–3647.
[4] L. Kaplan, J. W. Pavlik, K. E. Wilzbach, J. Am. Chem. Soc. 94 (1972) 3283–3284.
[5] U. C. Yoon, S. L. Quillen, P. S. Mariano, Tetrahedron Lett. 23 (1982) 919–922.
[6] U. C. Yoon, S. L. Quillen, P. S. Mariano, R. Swanson, J. L. Stavinoha, E. Bay, J. Am. Chem. Soc. 105 (1983) 1204–1218.
[7] R. Ling, M. Yoshida, P. S. Mariano, J. Org. Chem. 61 (1996) 4439-4449.
[8] S. J. Cho, R. Ling, A. Kim, P. S. Mariano, J. Org. Chem. 65 (2000) 1574–1577.
[9] F. Glarner, S. R. Thornton, D. Schärer, G. Bernardinelli, U. Burger, Helv. Chim. Acta 80 (1997) 121–127.
[10] E. A. Acar, F. Glarner, U. Burger, Helv. Chim. Acta 81 (1998) 81 1095–1104.
[11] F. Glarner, B. Acar, I. Etter, T. Damiano, E. A. Acar, G. Bernardinelli, U. Burger, Tetrahedron 56 (2000) 4311–4316.
[12] R. A. King, H. P. Lüthi, H. F. Schaefer III, F. Glarner, U. Burger, Chem. Eur. J. 7 (2001) 1734–1742.
[13] M. A. Clark, R. C. Schoenfeld, B. Ganem, J. Am. Chem. Soc. 123 (2001) 10425–10426.
[14] C. S. Penkett, I. D. Simpson, Tetrahedron Lett. 42 (2001) 1179–1181.
[15] C. S. Penkett, Synlett 1 (1999) 93–95.
[16] C. S. Penkett, I. D. Simpson, Tetrahedron 55 (1999) 6183–6204.
[17] R. Ling, P. S. Mariano, J. Org. Chem. 63 (1998) 6072–6076.
[18] Z. Zhao, L. Song, P. S. Mariano, Tetrahedron 61 (2005) 8888–8894.
[19] L. Song, E. N. Duesler, P. S. Mariano, J. Org. Chem. 69 (2004) 7284–7293.
[20] H. Lu, P. S. Mariano, Y. Lam, Tetrahedron Lett. 42 (2001) 4755–4757.
[21] X. H. Feng, E. N. Duesler, P. S. Mariano, J. Org. Chem. 70 (2005) 5618–5623.
[22] H. Lu, Z. Su, L. Song, P. S. Mariano, J. Org. Chem. 67 (2002) 3525–3528.
[23] For reviews, see: G. Poli, G. Prestat, Chemtracts: Org. Chem. 15 (2002) 506–513, and the next five references.
[24] T. Damiano, D. Morton, A. Nelson, Org. Biomol. Chem. 5 (2007) 2735–2752.
[25] J. Zou, P. S. Mariano, Photochem. Photobiol. Sci. 7 (2008) 393–404.
[26] S. Sowmiah, J. M. S. S. Esperança, L. P. N. Rebelo, C. A. M. Afonso, Org. Chem. Front. 5 (2018) 453–493.
[27] P. S. Mariano, Tetrahedron 39 (1983) 3845–3879.
[28] P. S. Mariano, Acc. Chem. Res. 16 (1983) 130–137.
[29] J. R. Vale, F. Siopa, P. S. Branco, C. A. M. Afonso, Eur. J. Org. Chem. (2016) 2048–2053.
[30] F. Siopa, J. P. M. António, C. A. M. Afonso, Org. Process Res. Dev. 22 (2018) 551–556.
[31] M. A. G. Fortunato, C.-P. Ly, F. Siopa, C. A. M. Afonso, Methods Protoc. 2 (2019) 67.
[32] C. Colombo, B. M. Pinto, A. Bernardi, A. J. Bennet, Org. Biomol. Chem.14 (2016) 6539–6553.
[33] For a recent example, see: Y. Liu, J. Oble, G. Poli, Beilstein J. Org. Chem. 15 (2019) 1107–1115;
[34] For a recent example, see: Y. Liu, Z. Mao, A. Pradal, P-Q. Huang, J. Oble, G. Poli, Org. Lett. 20 (2018) 4057–4061.
[35] For an account, see: C. Kammerer, G. Prestat, D. Madec, G. Poli, Acc. Chem. Res. 47 (2014) 3439–3447.
[36] For a chapter review, see: C. Kammerer-Pentier, F. Liron, G. Prestat, G. Poli, *Selectivity in Palladium Catalyzed Allylic Substitution. In Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*; Kazmaier, U., Ed.; *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin Heidelberg, 2012; Vol. 38, 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.
[41] T. Ohwada, H. Hirao, A. Ogawa, J. Org. Chem. 69 (2004) 7486-7494.
[42] R. Hadjadj-Aoul, A. Bouyacoub, A. Krallafa, F. Volatron, J. Mol. Struct. THEOCHEM 849 (2008) 8-16.
[43] I. Radić, N. Despotović, R. Vianello, Croat. Chem. Acta. 85 (2012) 495-504.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Carlos Alberto Matem Afonso

Carlos A. M. Afonso