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RESEARCH ARTICLE

Enantioselective Synthesis of 3-Heterosubstituted-2-amino-1-ols by Sequential Metal-free Diene Aziridination/Kinetic Resolution

Irene Giménez-Nueno,[a] Joan Guasch, [a] Ignacio Funes-Ardoiz, [b] Feliu Maseras, [b,c] M. Isabel Matheu, [a] Sergio Castillón*[a] and Yolanda Díaz*[a]

Abstract

A general protocol for the enantioselective synthesis of 3-heterosubstituted-2-amino-1-ols was developed based on metal-free intramolecular regio- and stereoselective diene aziridination and regioselective opening. Kinetic resolution of the resulting (1'-NR and 1'-SR)-4-oxazolidinones was performed using ABCs organocatalysts, expanding the application of this methodology.

Introduction

Vinylaziridines have recently emerged as important intermediates for the synthesis of pharmaceutical drugs and natural occurring products.[1] The thoroughly studied reactivity of the strained aziridine ring along with the possibility of later double bond functionalisation, make them versatile building blocks in organic synthesis.[2] General methods for the direct preparation of vinylaziridines include the Darzens-type reaction, the addition of allyl ylides or benzylsulfonium salts (Corey-Chaykvozky reaction) to imines, the ring-opening/closing of vinyl epoxides and the ring closing of 1,2-aminohalides (Scheme 1A).[2a,b] Moreover, the addition of a nitrene moiety into a conjugated diene has drawn much attention in the past few years (Scheme 1A).[3] In particular, remarkable examples on metal-catalysed intermolecular aziridination of conjugated double bonds in the presence of sulfamates,[4] sulfonamides,[1a,b] aryl azide[5] or [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs)[1c,d,6] as nitrene sources can be found at the literature. Common problems related to this approach are the control of the regioselectivity as well as the stereoselectivity, since *cis/trans* isomerization has been observed for some metals. Metal-catalysed intramolecular diene aziridination can overcome former regioselectivity issues. However, publications on this approach are scarce.[7] In addition, only few reports deal with the intermolecular metal-free preparation of vinylaziridines based on the use of $DppONH_2$/R_3N[8] and $PhthNNH_2$[9] (Scheme 1Bi), whereas there are no reports concerning the intramolecular version. Along these lines, metal-free aziridination of simple alkenes can be effected in the presence of $PhthNNH_2$/$PhI(OAc)_2$ system[10] or via *in situ* formation of intermediate iminoiodinane[11] (Scheme 1Bii).The intramolecular formation of aziridinium intermediates has also been described.[12]

The increased concern in developing greener processes for already known chemical transformations[13] has favoured the use of hypervalent iodine reagents as interesting surrogates of transition metal catalysts.[14] Thus, most of the processes for metal-free intramolecular aziridination are based on the use of I(III) reagents, and particularly iodosobenzene (PhIO).[11] Moreover, despite the current interest in metal-free alkene functionalisation, mechanistic studies regarding PhIO-mediated amination/aziridination reactions are still missing.

Within this context, our group became interested in the use of vinylaziridines as intermediates for the synthesis of unsaturated vicinal amino-alcohols related to relevant lipids occurring in nature.[6a,b] We have previously reported a rhodium-catalysed regio- and stereoselective oxyamination of dienes via tandem intramolecular aziridination/ring-opening (Scheme 1C).[7b]

Despite the outstanding control of the regioselectivity obtained at the ring opening step (S_N2 vs. S_N2'), based on the precise choice of the Rh catalyst, the method suffered from a lack of flexibility: the carboxylate ligands from hypervalent iodine reagent ($PhI(OR_2)_2$), released to the reaction medium, produced the *in situ* ring opening of the aziridine intermediate, thus preventing the discretional use of an external nucleophile.

As part of our interest in building-up a general protocol for synthesizing 3-heterosubstituted-2-amino-1-ol derivatives, we envisioned an intramolecular metal-free aziridination strategy amenable to be coupled with a sequential ring opening using an external nucleophile of choice (Scheme 1D). The resulting racemic oxazolidinones could be then subjected to an organocatalysed kinetic resolution applying a reported procedure by our group[15] to obtain enantioenriched synthetic intermediates bearing both the nucleophile and the amino moiety in a 1,2-array. Here we report our results on the one-pot PhIO mediated intramolecular aziridination/ring-opening of dienyl carbamates in the presence of *O*-, *N*-, *S*-nucleophiles and the generalisation of our BTM-catalysed kinetic resolution for substrates bearing alternative heteroatoms and groups adjacent to the oxazolidinone ring. A DFT mechanistic study on aziridine formation from PhIO as well as the final synthesis of two sphingosine analogues have also been performed.

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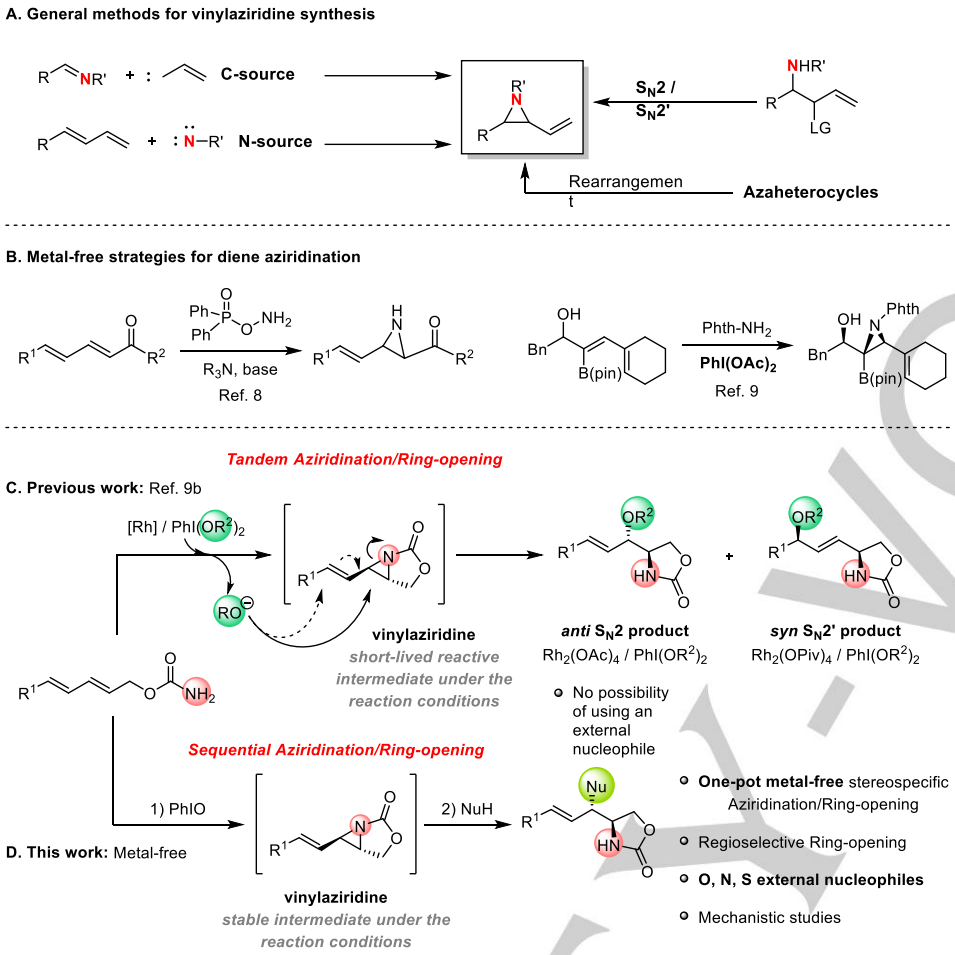

Scheme 1. A. General protocols for diene aziridination. B. Metal-free strategies for alkene aziridination. C. Consecutive metal-catalysed intramolecular aziridination/opening from dienyl carbamates. D. This work: Synthesis of vinyl-aziridines by metal-free intramolecular diene aziridination and *in situ* conversion into 3-substituted derivatives.

Results and Discussion

At the outset of this project, model carbamate **1** was initially treated with PhIO in the presence of 4Å molecular sieves to form vinylaziridine intermediate **(±)-2** which was directly opened in the reaction medium using methanol as a nucleophile to finally furnish the desired oxazolidinone **(±)-3** in an overall 56% NMR-yield as a single diastereomer with complete regiocontrol (Table 1, entry 1). Initial optimisation proved that solvent was a crucial factor for the final outcome of the reaction.[16] Chlorinated solvents gave the highest yields for the aziridination/ring-opening procedure (Table 1, entries 1 and 2) whereas oxazolidinone **(±)-3** was only formed up to 18% NMR-yield for all the other solvents tested (Table 1, entries 3-8). Working at higher concentrations (0.10 M of CH_2Cl_2) had a negative effect in conversion (Table 1, entry 9).

Disappointingly, alternative desiccant agents or different temperatures did not improve the final reaction yields (Table 1, entries 10-13). Therefore, only a moderate 61% NMR-yield over two steps was obtained after initial screening, even though complete consumption of starting material was confirmed by ^{1}H-NMR. Moreover, preliminary attempts to isolate oxazolidinone **(±)-3** resulted in an important decrease of yield due to product decomposition under prolonged contact with silicagel.

At this point, thorough analysis of the reaction crude NMR spectra revealed the presence of two by-products: chloro substituted oxazolidinone **(±)-4** (up to 20% NMR-yield) and a mixture of epoxides **(±)-5*trans*** and **(±)-5*cis*** (≤5% NMR-yield) (*see Table S1 in Supporting Information for a preliminary study on PhIO-mediated diene epoxidation*).

Whereas epoxide subproducts were consistently obtained in all reactions, the yield in the chloro derivative proved erratic and significantly varied depending of the substrate batch. Hence, we sought the proper conditions for optimal aziridination reaction, free of chlorinated subproducts. Chlorinated solvents have been reported to form either Cl radicals or HCl that *in situ* opened fused-ring intermediates with a similar chemical structure than vinylaziridine **(±)-2**.[17]

Taking into account this piece of information, PhIO-mediated aziridination was carried out in the presence of dibutylhydroxytoluene (butylated hydroxytoluene, BHT) as a radical scavenger. However, the final yield on **(±)-3** did not improve after overnight stirring while a relevant percentage of chlorinated oxazolidinone **(±)-4** was still generated (Table 1, entry 14).

Optimisation of the reaction conditions showed that recrystallisation of the apparently pure carbamate **1** resulted in a dramatic improvement in methoxy oxazolidinone **(±)-3** yield, formed in a remarkable 95% NMR-yield (70% isolated yield) (Table 1, entry 15).

We then became interested in testing alternative sources of hypervalent iodine reagent as oxidants for the intramolecular aziridination reaction. However, when carbamate **1** was reacted with $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ under the optimised conditions, no reaction or starting material decomposition, respectively, was observed (Table 1, entries 16 and 17).

Then, we carried out DFT calculations to clarify some of these experimental aspects. We used the M06-2X functional[18] and included the solvent implicitly by the SMD method (*see the Supporting Information for full computational details*).[19,20] We first analysed the difference between the I(III) sources. We computed the thermodynamics for the nitrene formation from the carbamate substrate **1** and each of the three precursors.[21] We used a trimeric structure of PhI=O as a model for the polymeric structure of this precursor (see Scheme 2).[22]

We found the transformation to be slightly endergonic for PhI=O (0.8 kcal/mol per nitrene unit). We consider that the use of molecular sieves in the experimental setup can be sufficient to displace the equilibrium towards the formation of the nitrene.

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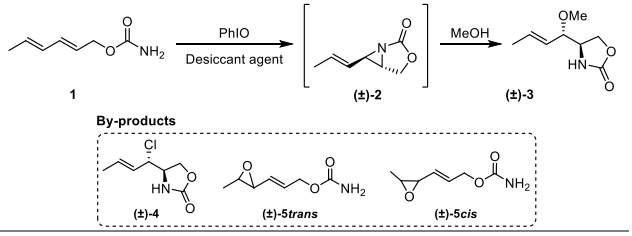
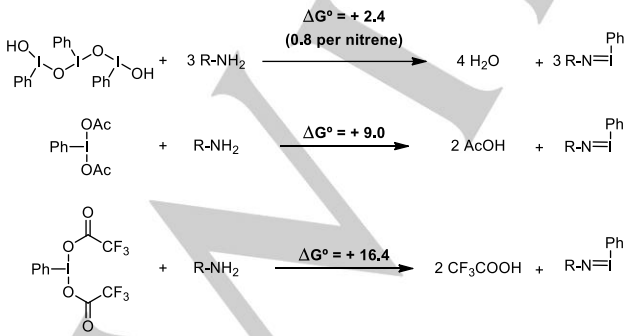
In contrast, the analogous process for both $PhI(OAc)_2$ and $PhI(COCF_3)_2$ was found to be significantly more endergonic, which agrees with the lack of experimental reactivity. We attribute this behaviour to the low basicity of the corresponding acetate or trifluoroacetate moieties in the PIDA and PIFA reactants.

Table 1. Intramolecular aziridination of dienyl carbamates **1** with PhIO. Optimisation of reaction conditions.[a]



Entry	Solvent (M)	Desiccant agent	Temp (ºC)	Yield (%)[b]
1	CH_2Cl_2 (0.04)	4Å M.S.	35	56
2	1,2-DCE (0.04)	4Å M.S.	35	61
3	CH_3CN (0.04)	4Å M.S.	35	18
4	Toluene (0.04)	4Å M.S.	35	15
5	Benzene (0.04)	4Å M.S.	35	13
6	CF_3-Benzene (0.04)	4Å M.S.	35	C.M.[c]
7	THF (0.04)	4Å M.S.	35	C.M.[c]
8	1,4-Dioxane (0.04)	4Å M.S.	35	C.M.[c]
9	CH_2Cl_2 (0.10)	4Å M.S.	35	18
10	CH_2Cl_2 (0.04)	$MgSO_4$	35	18
11	CH_2Cl_2 (0.04)	Na_2SO_4	35	14
12	CH_2Cl_2 (0.04)	4Å M.S.	r.t.	35
13	CH_2Cl_2 (0.04)	4Å M.S.	Reflux	52
14[d]	CH_2Cl_2 (0.04)	4Å M.S.	35	32
15[e]	CH_2Cl_2 (0.04)	4Å M.S.	35	95(70)
16[e,f]	CH_2Cl_2 (0.04)	-	35	-
17[e,g]	CH_2Cl_2 (0.04)	-	35	C.M.[c]

[a] Carbamate **1** (1 equiv.), PhIO (2 equiv.), desiccant agent (100 mg per 0.1 mmol carbamate **1**). MeOH as a quenching agent (2 mL). [b] Determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as an internal standard (isolated yield). [c] Complex mixture. [d] 10 mol% of radical inhibitor BHT. [e] Recrystallised carbamate **1** (1 equiv.). [f] $PhI(OAc)_2$ (2 equiv.). [g] $PhI(OCOCF_3)_2$ (2 equiv.).



Scheme 2. Thermodynamics of the iminoiodinane formation from PhIO trimeric structure, $PhI(OAc)_2$ or $PhI(OOCCF_3)_2$. and substrate **1** ($R\text{-}NH_2$ = **1**). Free energies in kcal/mol.

We also analysed computationally the detailed mechanism for the intramolecular nitrene transfer from intermediate **1t** (Figure 1). The first step is a conformational rearrangement from **1t** to **2t** *via* rotation around the C-O bond. From **2t**, we explored two different mechanisms for the aziridine formation: concerted (Figure 1, black) and bimolecular (Figure 1, grey). The bimolecular path was discarded due to the high free energy of the TS 5t-6t transition state (30.3 kcal/mol). A non-productive stepwise mechanism was also considered and dismissed (*see Supporting Information for details*).

Figure 1. Free energy profile of the aziridine formation from the iminoiodinane intermediate. Energies in kcal/mol.

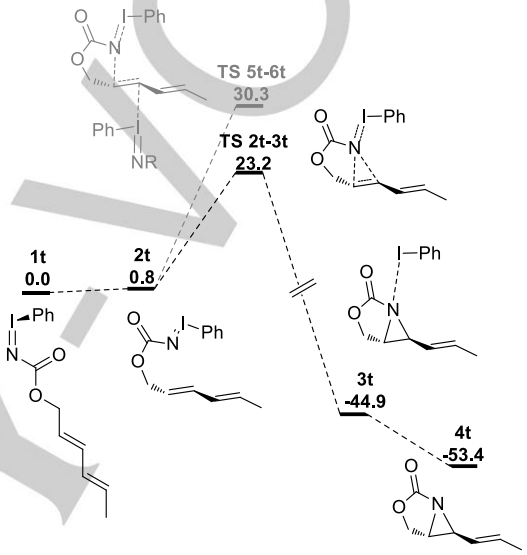
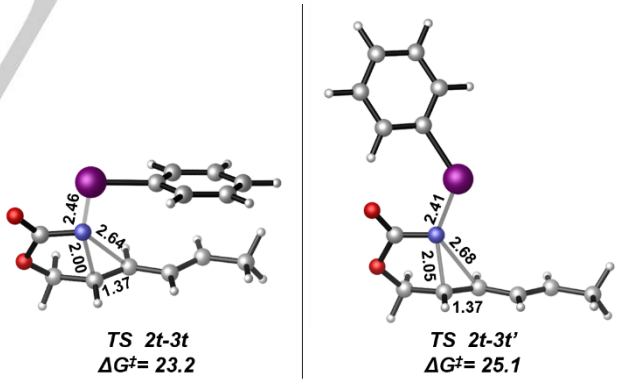


Figure 2. 3D Structures of the concerted transition states **TS 2t-3t** and the conformer **TS 2t-3t'**. Relevant bond distances in Å.



The concerted pathway has its highest free energy point (23.2 kcal/mol) at transition state **TS 2t-3t**. Interestingly, there are two conformers of the transition state: the most stable one (Figure 2, left) has a dispersion interaction between the phenyl group and the distal double bond of the substrate, while the least stable (Figure 2, right) has the phenyl group pointing out. We confirmed the concerted character of the preferred transition state *via* IRC calculation, although the aziridine formation is highly asynchronous. The N-C2 bond (on the O side of the substrate chain) is formed first. The asymmetry in the forming C-N bond lengths is 0.64 Å in the transition state. More details are giving in Figure S3 in the *Supporting Information*. The concerted character of the transition state, together with the presence of

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dispersion interactions, are promising hints towards the development of an enantioselective process using a chiral hypervalent iodine reagent.

Aziridination scope and subsequent opening with methanol was then studied for carbamates containing different side-chains **6-8** (Scheme 3). Reactions under the optimised conditions led to the aziridine intermediates **9-11**, as judged by TLC, which were sequentially opened by addition of methanol to give compounds **12-14** in good yields, although the aziridination step required longer reaction times or increased temperatures (Scheme 3).

As mentioned before, one of the main advantages of the present metal-free aziridination strategy is the possibility to select external nucleophiles to perform the ring-opening step, providing differently substituted oxazolidinones. According to previous strategies,[6a,23] several oxygen, nitrogen, and sulphur nucleophiles were chosen in order to explore the scope of the ring-opening step (Scheme 3). Moderate to high yields were achieved after optimisation of the reaction conditions for each nucleophile (*see Supporting Information for the complete optimisation study*).

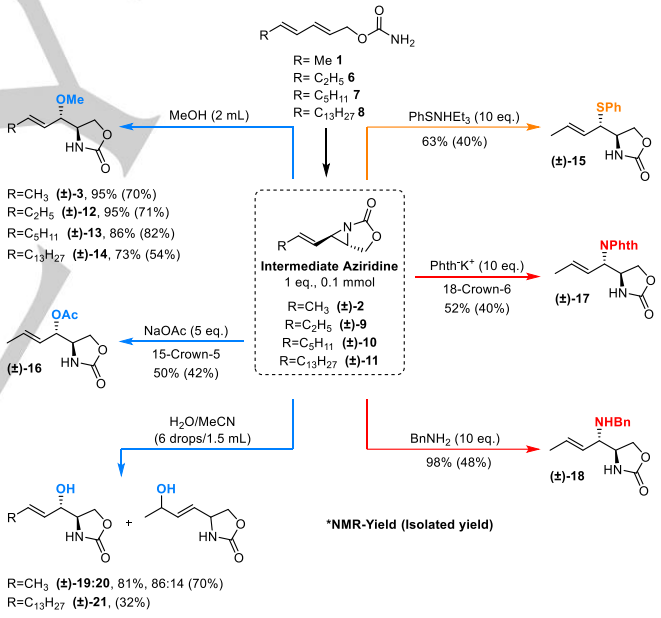
Initially, we tested the ring-opening step using water as a nucleophile in order to directly introduce the alcohol moiety. However, the molecular sieves present in the reaction medium trapped the water added, leading to low reaction yields. Driving the reaction in two different basic media (K_2CO_3, KOH), even in the presence of DMSO for avoiding the formation of a two-phase system, led to discouraging results (*See SI, Table S2*). Finally, hydroxy oxazolidinone **(±)-19** was generated along with a small percentage of the S_N2' ring-opening product **20** in a promising 70% overall yield using a mixture of H_2O in MeCN (*See SI, Table S2*). Likewise, long-chain oxazolidinone **(±)-21** was also prepared in 32% overall yield applying the same ring-opening strategy (Scheme 3). Moreover, another *O*-containing analogue, acetoxy oxazolidinone **(±)-16**, was synthesised using an excess of NaOAc salt in the presence of catalytic amounts of 15-crown-5 ether (*See SI, Table S3*) (Scheme 3).

For the introduction of *N*-nucleophiles, benzylamine and potassium phthalimide were selected. The ring-opening reaction proceeded smoothly when benzylamine was directly added to the reaction mixture, providing full conversion to oxazolidinone **(±)-18** which was isolated in a 48% yield over two steps, due to product decomposition during column chromatography (Scheme 3). Phthalimide, however, was a more challenging nucleophile that required an intense optimisation work (*See SI, Table S4*). The best results were obtained upon treatment of vinyl aziridine intermediate **(±)-2** with potassium phthalimide and catalytic amounts of 18-crown-6 ether, to furnish oxazolidinone **(±)-17** in a 40% overall yield (Scheme 3).

Finally, thiophenol was selected to illustrate the ring-opening step with *S*-containing nucleophiles. Preliminary results suggested that the soft and slightly acid character of this nucleophile favoured S_N2' ring-opening product over the S_N2 oxazolidinone **(±)-15** (*See SI, Table S5*). In fact, slow addition of PhSH led to a substantial increase in the formation of S_N2 product **(±)-15**. Then, considering previous ring-opening examples, NaSPh salt was tested as nucleophile for the ring opening step (*See SI, Table S5*). However, no nucleophile incorporation was observed when intermediate vinyl aziridine **(±)-2** was directly treated with the solid salt. Attempts to solubilise NaSPh in different organic solvents were unsuccessful. However, the addition of catalytic amounts of 15-crown-5 ether triggered PhSNa solubilisation and nucleophilicity providing the desired oxazolidinone **(±)-15** in a 55% yield for two steps. Further improvement of the ring-opening yield was achieved by switching to $PhSNHEt_3$ as the nucleophile, furnishing oxazolidinone **(±)-15** in a 63% yield (40% isolated yield).

As part of our increased interest on the synthesis of sphingolipid analogues as potential SK1 inhibitors for cancer treatment, we envisioned the possibility of applying the PhIO-mediated aziridination/ring-opening methodology to the preparation of new sphingosine analogues bearing substituents in a *syn*-relative configuration starting from (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate **27** (Scheme 4). The synthesis of this starting material was accomplished through a four-step procedure from commercially available propargyl alcohol **22.** Initial carbamoylation reaction followed by a Sonogashira coupling with *trans*-1 bromo-1-propene[6b] gave access to enyne carbamate **24**. Subsequent platinum-catalysed hydrosilylation reaction[24] furnished a mixture of *E*-silylenones **25** and **26**, which were finally treated with TBAF to afford **27** (Scheme 4a).

The recrystallised (2*Z*,4*E*)-dienyl carbamate **27** was then submitted to the PhIO-mediated aziridination reaction under the optimised conditions to give vinylaziridine **(±)-28**, which was subsequently treated with the same set of nucleophiles used for the ring-opening step of **(±)-2** to afford compounds **(±)-29-33** (Scheme 4b). In general, final oxazolidinone yields were lower than those previously observed for 2*E*,4*E* dienyl carbamate **1**.



Scheme 3. Aziridination of carbamates **1**,**6-8** and opening of vinylaziridines **(±)-2**, **9-11** to give 3-OR-, 3-NR^1R^2-, 3-SPh- and 2-amino-4-ene-1-ols.

Looking for an explanation for this fact, we also explored computationally the mechanism of the *2Z,4E* substrate **27**. In this case, the free energy barrier for the aziridine formation is 26.4 kcal/mol, 3.2 kcal/mol higher than that from the corresponding *2E,4E* substrate (*see Figure S4 in the Supporting Information*), which may be the reason for observed lower yields. This higher barrier can be rationalized due to the lack of the dispersion interaction between the PhI moiety and the second double bond.

Especially notorious was the case of phenyl sulfanyl oxazolidinone **(±)-33** (Scheme 4b). When the optimised $PhSNHEt_3$ salt was used as a nucleophile, oxazolidinone **(±)-33** was not obtained. By switching the nucleophile to a mixture of

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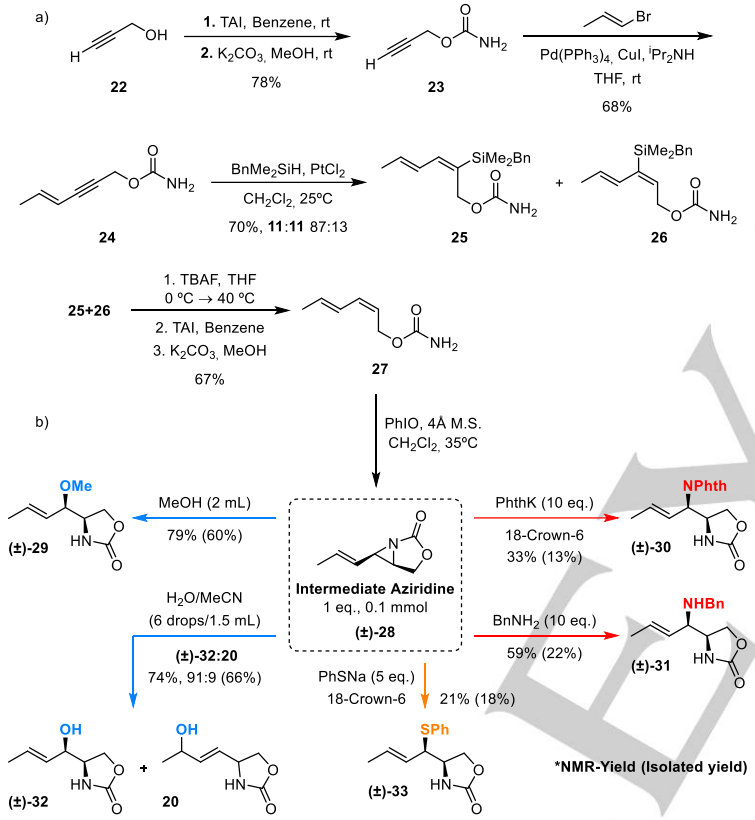
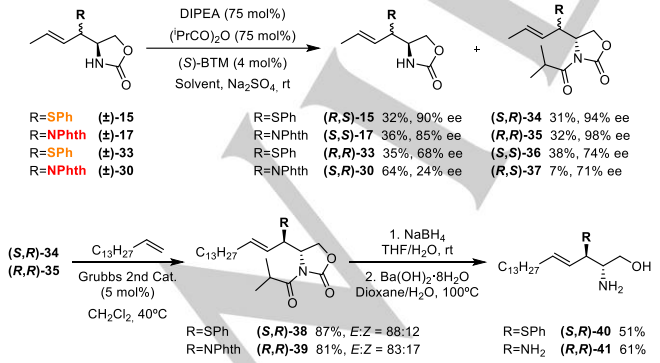
NaSPh and catalytic amounts of 15-crown-5 ether, we were able to form product **(±)-33**, although in low yields. Nevertheless, all oxazolidinone products were isolated as single diastereomers. *Syn*-configuration was assigned based on the different chemical shifts and coupling constants of the oxazolidinone ring in this series when compared to the NMR-spectra of related *anti*-products. The formation of diastereomerically pure *anti*- or *syn*-products from both the *E,E- and the Z,E* dienyl carbamates, respectively, accounts for the stereospecificity of the whole process, involving the alkene aziridination but also the ring opening.



Scheme 4. a) Synthesis of cis-trans-dienylcarbamate **27**. b) *One-pot* aziridination/ring-opening of carbamate **27** with *O*-, *N*- and *S*-nucleophiles.



Scheme 5. Kinetic resolution of intermediate *anti*-oxazolidinones **(±)-15**, **(±)-17** and *syn*-oxazolidinones **(±)-30**, **(±)-33** and final synthesis of sphingosine analogues **(*S*,*R*)-40** and **(*R*,*R*)-41** via cross-metathesis and deprotection.

We have recently reported an efficient BTM-catalysed kinetic resolution of several *O*-acyl protected hydroxy oxazolidinones via an enantioselective *N*-acylation of the corresponding lactame.[15,25] The interaction between the carbonyl moiety present at the protecting group and the heterocyclic thiazolium cation formed after the initial acylation of the BTM catalyst favoured the stabilisation of the reactive transition state. We hypothesised that *S*- and *N*-containing oxazolidinones could also be used as starting materials for the former kinetic resolution since the PhS group, or the carbonyl moieties from phthalimide group, could favour the stabilisation of the transition state in a similar way. Thus, *S*-substituted oxazolidinones, **(±)-15** and **(±)-33**, and *N*-substituted oxazolidinones, **(±)-17** and **(±)-30**, previously obtained from the PhIO mediated aziridination/ring-opening methodology, were submitted to kinetic resolution conditions using (*S*)-BTM as catalyst (Scheme 5). To our delight, both *anti*-oxazolidinones **(±)-15** and **(±)-17** underwent the kinetic resolution in good yields and remarkable enantioselectivities, 94% ee and 98% ee for the acylated products **(*S*,*R*)-34** and **(*S*,*R*)-35** and 90% ee and 85% ee for the recovered starting material **(*R*,*S*)-15** and **(*R*,*S*)-17**, respectively. However, only moderate selectivities were observed for the *syn*-*S*-substituted oxazolidinone **(±)-33** whereas *syn*-*N*-substituted oxazolidinone **(±)-30** proved to be mainly unreactive under the kinetic resolution conditions due to its low solubility in the reaction medium. With the aim of exploiting this methodology in the synthesis of biologically relevant molecules such as sphingosine analogues, the enantioenriched acylated oxazolidinones were further elaborated via a cross-metathesis reaction to introduce the characteristic aliphatic chain of these natural products. Only *anti*-substituted oxazolidinones **(*S*,*R*)-34** and **(*R*,*R*)-35** rendered the desired elongated products **(*S*,*R*)-38** and **(*R*,*R*)-39** when they were treated under optimised cross-metathesis conditions (Scheme 5).[14] The reason for this lack of reactivity of *syn* isomers is not clear and has not been addressed but could be due to steric clash between the catalyst and the syn-heteroatomic substituted oxazolidinone.

Deprotection of the terminal amino-alcohol moiety was accomplished to finally obtain two enantioenriched sphingosine analogues with the same configuration than that of the natural occurring product bearing a thiophenol group **(*S*,*R*)-40** and a primary amine **(*R*,*R*)-41** at the 3-position respectively (Scheme 5).

Conclusions

A general protocol for accessing (1'-OR, 1'-NR and 1'-SR)-4-oxazolidinones in a regio- and stereoselective manner was developed based on a metal-free intramolecular aziridination of dienyl carbamates to give vinylaziridines and subsequent opening with the corresponding nucleophiles. This method could be expanded to the introduction of carbon nucleophiles.[23] The organocatalyzed kinetic resolution of the so obtained racemic oxazolidinones gives access to enantioenriched 3-NHR- and 3-SR-2-amino-4-ene-1-ols. This general protocol was applied to the enantioenriched synthesis of (2*S*,3*R*)-3-deoxy-3-SPh- and (2*R*,3*R*)-3-amino-3-deoxy-sphingosine derivatives via cross-metathesis reaction and removal of protecting groups. A DFT mechanistic study on PhIO promoted aziridination is also

provided, including an explanation for the remarkable performance of PhIO over other related I(III) reagents for this transformation.

Experimental Section

General procedure for one-pot PhIO mediated Aziridination/Ring-Opening. A flame dried Schlenk containing a magnetic stirring bar was charged with activated 4Å M.S. (100 mg / 0.1 mmol carbamate) in distilled CH_2Cl_2 (0.04M) under argon atmosphere. Dienyl carbamate (0.1 mmol) and PhIO (0.2 mmol) were added and the heterogeneous mixture was stirred at 35ºC unless stated in the specific procedure until TLC showed complete consumption of the starting material. Nucleophile was then added and the reaction mixture was stirred overnight. The crude solution was filtered over celite, abundantly washed with CH_2Cl_2 and concentrated under reduced pressure. The yield over the two steps was determined by ^{1}H-NMR spectroscopy, using 1,3-dinitrobenzene as internal standard. The reaction crude was initially purified through a short column chromatography (2-3 cm) in order to avoid product decomposition under prolonged contact with silicagel.

General procedure for the BTM-catalysed kinetic resolution of oxazolidinones with isobutyric anhydride. The reactions were set at the globe box. The catalyst was used within a solution which was prepared by dissolving (*S*)-BTM (10.1 mg, 0.04 mmol) and DIPEA (131 µL, 0.75 mmol) in $CHCl_3$ (4.9 mL). One dram vial
was charged with the oxazolidinone substrate (0.10 mmol) and 0.5 mL of the catalyst solution. Then 100 mg of Na_2SO_4 were added and the reaction mixture was magnetically stirred for 5 min before being treated with isobutyric anhydride (0.075 mmol). The reaction mixture was kept under stirring and followed by ^{1}H NMR. Methanol was finally added to quench the reaction.

General procedure for the *N*-acylation of racemic oxazolidinones with isobutyric anhydride.[26] Oxazolidinone (0.10 mmol) was dissolved in CH_2Cl_2 (0.1 M) at room temperature under argon atmosphere. Et_3N (0.10 mmol) was then added and the solution was cooled to 0ºC. Stirring was continued for approximately 20 min and DMAP (2.5 mol%) and (^{i}PrCO$_2$)O (0.11 mmol) were subsequently added. The resulting mixture was kept at 0ºC for one hour and then warmed to room temperature. After completion, the crude was concentrated under reduced pressure.

General procedure for the cross metathesis of alkenyl oxazolidinones with terminal olefins.[15] A two-neck round-bottom flask fitted with a reflux condenser was charged with a solution of alkenyl oxazolidinone (0.10 mmol) in dry dichloromethane (0.05 M). Terminal olefin (0.12 mmol) and Grubbs catalyst 2nd generation (5 mol%) were then added and the reaction mixture was stirred at 40ºC for 24 h. After completion, the crude was concentrated under reduced pressure.

Computational Methods

All the calculations were performed using Gaussian09 program package (Rev. D01).[27] We chose the M06-2X method[28] based on its well-recognized accuracy in iodine(III) chemistry.[29] In addition, all the structures were optimized in solution considering the experimental solvent (dichloromethane, ε = 4.7113) implicitly through the SMD implicit solvation method.[30] We carried out the optimizations and frequency calculations using the following basis set: 6-31G(d) for C, H, N and O atoms[31] and LANL2DZ(d,p) for iodine atom. Additionally, potential energies were further refined using the 6-311++G(d,p) basis set for C, H, N and O (keeping the same basis set for iodine).[32]

All the stationary points were characterized as minima or as transition states by frequency analyses (zero imaginary frequencies for minima and one for transition states). Transition states were connected towards reactants and products using IRC calculation when needed. All the energies shown along the manuscript are free energies in solution calculated at standard conditions (298 K and 1 atm) and in kcal/mol. A data set collection of computational results is available in IoChem-BD repository.[33]

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest

Keywords: vinylaziridines synthesis• metal-free aziridination • carbamates kinetic resolution • organocatalysis • ABC catalysts • enantioselectivity • sphingosine analogues

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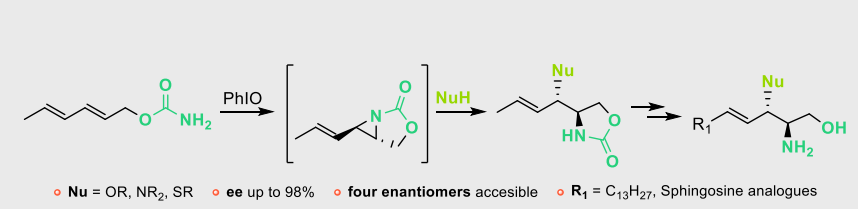
RESEACH ARTICLE



Metal-free intramolecular aziridination of dienyl carbamates afforded vinylaziridines that were opened with different nucleophiles. Kinetic resolution via ABC-catalysed acylation of the so obtained racemic oxazolidinones allows to stablish a general protocol for obtaining 3-heterosubstituted 2-aminoalcohols with high enantioselectivity. The efficiency of this methodology was demonstrated by preparing enantioenriched (2*S*,3*R*)-3-deoxy-3-SPh- and (2*R*,3*R*)-3-amino-3-deoxy-sphingosine derivatives.

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Enantioselective synthesis of 3-Heterosubstituted-2-amino-1-ols by sequential metal-free diene aziridination/kinetic resolution