Diastereoselective synthesis of 6-functionalized 4-aryl-1,3-oxazinan-2-ones and their application in the synthesis of 3-aryl-1,3-aminoalcohols and 6-arylpiperidine-2,4-diones

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Graphical abstract

Abstract

Halocyclocarbamation of benzyl N-(1-phenyl-3-butenyl)carbamates afforded 6-functionalized 4-aryl-1,3-oxazinan-2-ones with moderate to excellent diastereoselectivity depending on the N-substituent. Importantly, in contrast to reported cyclocarbamations of homoallylic carbamates which are generally trans-diastereoselective, cyclization of N-unsubstituted Cbz-protected homoallylamines led to cis-1,3-oxazinan-2-ones, predominantly. The use of N-benzylated and in situ prepared N-silylated derivatives resulted however in trans-selectivity. Transition states are proposed to explain the stereochemical influence of the N-substituent on the cyclocarbamations. The functionalized 1,3-oxazinan-2-ones could be further elaborated

Keywords: cyclocarbamation, 1,3-oxazinan-2-ones, 1,3-amino alcohols, piperidine-2,4-diones

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towards biologically or synthetically important 6-arylpiperidine-2,4-diones and 3-aryl-1,3-aminoalcohols.

1. Introduction

1,3-Oxazinan-2-ones form an important class of heterocyclic compounds which have been studied for their biological activities,¹ showing antibacterial,² anti-inflammatory,³ anti-HIV,⁴ and antithrombotic activities.⁵ Furthermore, 1,3-oxazinan-2-ones are useful compounds for further synthetic transformations to natural products⁶ or biologically relevant compounds,⁷ and are naturally occurring compounds, e.g. the maytansinoid antitumor compounds.⁸ The closely related 1,3-aminoalcohols, which are suitable precursors of 1,3-oxazinanones,⁹ as well as derived products from the latter heterocycles,¹⁰ have found wide application as ligands, auxiliaries and phase transfer catalysts in organic chemistry.¹¹ One of the two most important methods for the asymmetric synthesis of 1,3-oxazinan-2-ones, next to halocyclocarbamation of chiral homoallylic carbamates,⁶a,e-h,¹⁰ involves cyclization of chiral 1,3-aminoalcohols.⁷a,9a-c,e More specifically, the 3-phenyl-1,3-aminoalcohol moiety is an important C3-unit present in naturally occurring products, such as (-)-cytoxazone (1),¹² (-)-codonopsinine (2),¹³ the lythraceous alkaloids (-)-lasubine I (3), (-)-lasubine II (4),¹⁴ and vertine (cryogenine) (5) with ataractic, anti-inflammatory, antispasmodic and antimalarial activity.¹⁵ Other examples are 1,2-diphenyl substituted diphenylpyraline derivatives cis-6 and trans-6 with good antimycobacterial activity,¹⁶ the vesicular monoamine transporter type 2 (VMAT2) antagonist dihydrotetrazenazine (DTBZ) as a potent hypoglycemic agent,¹⁷ and (S)-dapoxetine (7), which is used for treatment of premature ejaculation and is structurally related to fluoxetine (Prozac) (8).¹⁸ Moreover, 3-phenyl-1,3-aminoalcohols are also useful in the synthesis of drug-like azetidines,¹⁹ and piperidines.²⁰ Very recently it was shown that anti-2-alkoxy-3-amino-3-arylpropan-1-ols and the corresponding ring closed cis-5-alkoxy-4-aryl-1,3-oxazinanes are promising new types of antimalarial agents.²¹

In the present article, the results of an extensive study on the diastereoselective electrophile-induced cyclocarbamation of different N-protected benzyl N-(1-phenyl-3-butenyl)carbamates towards the synthesis of cis- or trans-6-(bromomethyl)-, 6-(iodomethyl)- and 6-(phenylselenomethyl)-4-phenyl-1,3-oxazinan-2-ones are disclosed. These oxazinan-2-ones represent versatile intermediates for the synthesis of functionalized 3-aryl-1,3-aminoalcohols and 6-arylpiperidine-2,4-diones.
2. Results and discussion

Despite the fact that electrophile-induced cyclocarbamation of homoallylic carbamates to 4,6-disubstituted 1,3-oxazinan-2-ones has been reported regularly in organic synthesis, the method has not been developed in a general sense. Mostly trans-4,6-disubstituted oxazinanones are prepared starting from fully N-substituted homoallylic carbamates without the development of a selective preparative method to the cis-diastereomers. Moreover, a lack of diastereoselectivity in some cyclocarbamations detracts from synthetic utility. Benzyl N-(1-phenyl-3-butenyl)carbamates 9 were prepared according to a recently described iodine-catalyzed three-component condensation of benzaldehydes, benzylcarbamate and allyltrimethylsilane, as suitable starting materials for further diastereoselective electrophile-induced cyclocarbamation to 6-functionalized cis- and trans-4-phenyl-1,3-oxazinan-2-ones 10.

The benzyl N-(1-phenyl-3-butenyl)carbamates 9 with a free NH group were directly submitted to cyclocarbamation with bromine, iodine or phenylselenyl bromide in dichloromethane, furnishing the desired cis- and trans-4-aryl-1,3-oxazinan-2-ones 10a-f in 79-90% yield after crystallisation with low to good cis-diastereoselectivity (Scheme 1). A decreasing cis/trans ratio from 80:20 to 54:46 was observed as the steric demand of the 6-substituent increases from CH2Br to CH2SePh. Column chromatography on silica gel allowed the isolation of the major cis-6-(bromomethyl)- and 6-(iodomethyl)-4-phenyl-1,3-oxazinan-2-ones 10a-d as diastereomerically pure compounds in acceptable yields (29-42%) together
with the pure trans-isomers 10a-d (7-16% yield). This result forms one of the few examples
in which 4,6-disubstituted 1,3-oxazinan-2-ones resulting from a cis-stereoselective
halocyclocarbamation have been isolated in a preparatively useful manner. The structural
assignment of the cis- and trans-isomers 10 is based on analysis of the values of the vicinal
coupling constants $(\text{J}_{\text{HH}})$ of H4, H5, H5’ and H6 (Figure 1). The 6-substituent occupies an
equatorial position both in the cis- and trans-isomers 10 as demonstrated by the typical large
coupling constants $\text{J}_{\text{H6,H5}} = 9.0 – 11.6$ Hz for the axial protons H5 and H6.10b,22a For the cis-
isomers 10, a large coupling constant $\text{J}_{\text{H4,H5}} = 11.3 – 11.6$ Hz for H4 and H5 in axial
positions is also observed. The structure and the stereochemical arrangement of cis-6-
(bromomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one 10b was unambiguously
determined by X-ray diffraction analysis (Figure 2).

Scheme 1.

Figure 1. Selected coupling constants for cis- and trans-oxazinanones 10
Bromocyclocarbamation of homoallylamine 9a with N-bromosuccinimide in dichloromethane afforded cis- and trans-6-(bromomethyl)-4-phenyl-1,3-oxazinan-2-ones 10a in a good cis/trans ratio of 9:1 (Scheme 2). However, the reaction time increased to 48 hours and the yield dropped to 74% after extractive work up with 2M aq. NaOH and crystallization from dichloromethane and hexane. The latter steps were necessary to convert the unstable intermediate 2-benzyloxy-6-(bromomethyl)-4-phenyl-5,6-dihydro-4H-[1,3]oxazines into the 1,3-oxazinan-2-ones 10a and to remove the formed succinimide and benzyl alcohol. An attempted chlorocyclocarbamation of homoallylamine 9b with N-chlorosuccinimide failed, as no reaction occurred upon stirring carbamate 9b with 1.22 equiv NCS at room temperature in dichloromethane for 10 days.

Scheme 2.

The diastereoselectivity of the cyclocarbamation of the benzyl N-(1-phenyl-3-butenyl)carbamates 9 was nicely reversed after in situ protection of the homoallylamines 9 with a tert-butyldimethylsilyl (TBDMS) group. Treatment of the homoallylamines 9 with TBDMS triflate in the presence of 2,6-lutidine in dichloromethane at 0 °C for 2 hours, followed by reaction with excess of bromine, iodine or phenylselenyl bromide at 0 °C for 16 –
24 hours afforded the cis- and trans-4-aryl-1,3-oxazinan-2-ones 10a-f in 71-76% yield after crystallisation with trans-diastereoselectivity (Scheme 3). In the bromocyclocarbamation of benzyl N-1-(4-methoxyphenyl)-3-butylcarbamates 9b, the typical excess of 2.44 equiv of electrophile was lowered to 2.05 equiv of Br₂ to avoid bromination in the ortho-position of the aromatic methoxy substituent. The highest trans-diastereoselectivity, up to trans/cis ratio 9:1, was obtained in the iodocyclocarbamation to 6-(iodomethyl)-4-phenyl-1,3-oxazinan-2-ones 10c,d. A slight trans-selectivity was observed for the selenides 10e,f.

\[
\begin{align*}
10a (R^1 = H, E = Br, 76%, \text{dr cis/trans } 24:76) \\
10b (R^1 = OMe, E = Br, 73%, \text{dr cis/trans } 30:70) \\
10c (R^1 = H, E = I, 71%, \text{dr cis/trans } 10:90) \\
10d (R^1 = OMe, E = I, 75%, \text{dr cis/trans } 15:85) \\
10e (R^1 = H, E = SePh, 73%, \text{dr cis/trans } 46:54) \\
10f (R^1 = OMe, E = SePh, 71%, \text{dr cis/trans } 44:56)
\end{align*}
\]

\[\text{Scheme 3.}\]

Similarly, the N-benzyl-substituted homoallylamines 11, prepared in 65-70% yield by protection of homoallylamines 9 with benzyl iodide after deprotonation with NaH in DMF,²⁵ underwent cyclocarbamation with zero to excellent trans-diastereoselectivity (trans/cis ratio from 50:50 to 94:6).⁶ The trans- and cis-4-aryl-3-benzyl-1,3-oxazinan-2-ones 12a-f were obtained in 78-86% yield after column chromatography (Scheme 4).

\[
\begin{align*}
12a (R^1 = H, E = Br, 86%, \text{dr cis/trans } 11:89) \\
12b (R^1 = OMe, E = Br, 85%, \text{dr cis/trans } 15:85) \\
12c (R^1 = H, E = I, 85%, \text{dr cis/trans } 6:94) \\
12d (R^1 = OMe, E = I, 86%, \text{dr cis/trans } 9:91) \\
12e (R^1 = H, E = SePh, 78%, \text{dr cis/trans } 33:67) \\
12f (R^1 = OMe, E = SePh, 82%, \text{dr cis/trans } 50:50)
\end{align*}
\]

\[\text{Scheme 4.}\]
The *cis*-stereoselectivity of the cyclocarbamation reactions of the N-monosubstituted homoallylamines 9 can be explained on the basis of the conformational arrangement in the proposed transition state of the reaction (Figure 3). The major *cis*-1,3-oxazinan-2-ones 10 are probably formed through half-chair type transition state 13 in which both the alkene moiety, undergoing the *anti*-attack of the carbonyl oxygen, as well as the 4-aryl substituent adopt pseudoequatorial positions with only minor 1,2-strain between the N-H substituent and the neighbouring 4-aryl substituent. The introduction of a second substituent on nitrogen, either via *in situ* N-silylation of carbamates 9 with TBDMSOTf or via N-benzylation to carbamates 11, forces the 4-aryl substituent to adopt a pseudoaxial position. In this way the 1,2-strain with the neighbouring N-TBDMS or N-benzyl substituent is minimized in transition state 14 resulting in a small 1,3-diaxial interaction, and the formation of the *trans*-1,3-oxazinanones 10 and 12 is preferred.

![Figure 3. Possible transition states in the formation of the *cis*- and *trans*-diastereomers 10 and 12](image)

Having the functionalized 1,3-oxazinan-2-ones 10 in hand, their synthetic potential was studied under different conditions. A typical attempt to hydrolyze the 6-(iodomethyl)-1,3-oxazinan-2-ones 10c,d directly to the corresponding 1,3-aminoalcohols, afforded an unexpected but interesting new synthesis of 6-arylpiperidine-2,4-diones. Treatment of 4-aryl-6-(iodomethyl)-1,3-oxazinan-2-ones 10c,d with an aqueous solution of sodium hydroxide under reflux in ethanol afforded the 6-arylpiperidine-2,4-diones 15 in 82-86% yield after
recrystallisation (Scheme 5). 6-Arylpiperidine-2,4-diones have been prepared as analogues of VMAT2 antagonists, and represent key intermediates for further synthetic transformations to 6-aryl-4-hydroxyxypiperidin-2-ones, 4-hydroxyxyppecolic acids, (R)-(−)-2-phenylpiperidine, and biomimetic NADH models. Relatively few methods for the synthesis of 6-arylpiperidine-2,4-diones have been reported in the literature. An important method is the coupling of β-aryl-β-amino esters with alkyl malonates, followed by Dieckmann condensation, hydrolysis and decarboxylation. Alternatively, β-aryl-β-amino acid derivatives can be reacted with metal enolates of alkyl acetates or with Meldrum’s acid in the presence of pyridine to afford the corresponding δ-amino-β-keto esters which are subsequently cyclized under basic conditions to give 6-arylpiperidine-2,4-diones. Analogously, a number of 6-arylpiperidine-2,4-diones were obtained by reaction of chiral N-sulfinyl imines with lithium or TMS dienolates of 2,2,6-trimethyl-1,3-dioxin-4-one. An early efficient preparation of 1-tert-butyl-6-phenylpiperidine-2,4-dione involved the addition of N-benzylidene-tert-butylamine to diketene. 1-Methyl-6-phenylpiperidine-2,4-dione was synthesized in moderate yield through 1,3-dipolar cycloaddition of the appropriate nitroene with methyl 2-chlorobut-3-enoate and subsequent hydrogenolysis of the intermediate isoxazolidine. 6-Arylpiperidine-2,4-diones are also accessible by acid hydrolysis of the cycloadducts obtained through aza-Diels-Alder reaction of 1,3-dimethoxy-1-(trimethylsiloxy)butadiene (Brassard’s diene) with aromatic aldimines. The formation of piperidine-2,4-diones from 6-(iodomethyl)-1,3-oxazinan-2-ones is believed to proceed via initial base-induced elimination of hydrogen iodide to give 6-methylene-1,3-oxazinan-2-ones followed by basic hydrolysis of the oxazinanone and intramolecular C-carbamoylation of the formed enolate. The alkoxide-catalyzed rearrangement of isomeric 2-alkylidene-1,3-oxazinan-6-ones to piperidine-2,4-diones has been described more than 40 years ago. On the other hand, to the best of our knowledge, the rearrangement of 6-alkylidene-1,3-oxazinan-2-ones to piperidine-2,4-diones has never been reported. Alternatively, the iodo substituent in 6-(iodomethyl)-1,3-oxazinan-2-ones could be successfully substituted upon heating with sodium azide in DMSO which efficiently afforded the corresponding 6-(azidomethyl)-1,3-oxazinan-2-ones (Scheme 5). The absence of a tethered leaving group in the C-6 substituent of 6-(azidomethyl)-1,3-oxazinan-2-ones, inhibiting base-induced elimination to 6-methylene-1,3-oxazinan-2-ones, allowed the solvolysis to 4-amino-4-aryl-1-azidobutan-2-ols (81-90% yield) upon heating with sodium methoxide in methanol. Upon considering the aryl group as a carboxyl synthon, the azido aminoalcohols are of potential interest for further synthetic elaboration as they incorporate
the scaffold of the naturally occurring nonproteinogenic amino acids 4-hydroxyornithine and 4-hydroxyarginine, which are also constituents of the antibiotic cyclopeptide natural products biphenomycins, K-582 type antibiotics, and β-lactam antibiotic clavalanine.

![Scheme 5](image)

Similarly, the 6-(phenylselanylmethyl)-1,3-oxazinan-2-ones 10e,f were easily solvolyzed to the corresponding 4-amino-4-aryl-1-(phenylselanyl)butan-2-ols 19 (80-84% yield) (Scheme 6). The latter 1,3-aminoalcohols 19 are of synthetic interest in view of the versatile chemistry of organoselenium compounds.

![Scheme 6](image)

3. Conclusion
In conclusion, an efficient synthesis of 6-functionalized 4-aryl-1,3-oxazinan-2-ones has been achieved based on electrophile-induced cyclocarbamation of benzyl $N$-(1-phenyl-3-butenyl)carbamates. Most importantly, stereochemically pure cis-6-(bromomethyl)- and 6-(iodomethyl)-4-phenyl-1,3-oxazinan-2-ones became accessible via cyclization of $N$-unsubstituted Cbz-protected homoallylamines. On the other hand, the use of $N$-benzylated and in situ prepared $N$-silylated derivatives resulted in cyclocarbamation with trans-selectivity. Furthermore, the functionalized 1,3-oxazinan-2-ones could be elaborated towards biologically or synthetically important 6-arylpiperidine-2,4-diones and 3-aryl-1,3-aminoalcohols.

4. Experimental

4.1. General

$^1$H NMR spectra were recorded at 300 MHz with CDCl$_3$ as solvent and tetramethylsilane as internal standard. $^{13}$C NMR spectra were recorded at 75MHz with CDCl$_3$ as solvent. Dichloromethane was distilled over CaH$_2$, DMF was distilled and kept over molecular sieves, methanol was dried by reaction with magnesium and distilled, while other solvents were used as received from the supplier.

4.2. Synthetic procedures

4.2.1. Synthesis of benzyl $N$-(1-phenyl-3-butenyl)carbamates 9. Benzyl $N$-(1-phenyl-3-butenyl)carbamates 9 were prepared according to a literature procedure.$^{23}$

4.2.2. General procedure for the preparation of 4-aryl-1,3-oxazinan-2-ones 10. A solution of electrophile (1.22 mmol) (Br$_2$, I$_2$, PhSeBr) in freshly distilled dry dichloromethane (10 mL) was added dropwise in a period of 10 minutes to a stirred solution of benzyl $N$-(1-phenyl-3-butenyl)carbamate 9 (1.0 mmol) in dichloromethane (20 mL) and the mixture was stirred at room temperature under nitrogen atmosphere for 16 – 24 hours. The reaction was quenched with 2 N aq. Na$_2$SO$_3$ (for reaction with Br$_2$) or 2 N aq. Na$_2$S$_2$O$_3$ (for reaction with I$_2$) or brine (for reaction with PhSeBr). The mixture was extracted with dichloromethane, dried (MgSO$_4$), filtered, evaporated under reduced pressure and the residue was crystallized from diethyl ether/hexane to afford 4-aryl-1,3-oxazinan-2-ones 10 as a mixture of cis- and trans-isomers.
4.2.3. *cis*-6-(Bromomethyl)-4-phenyl-1,3-oxazinan-2-one (10a). Isolated by column chromatography (diethyl ether). Amorphous white solid; mp: 183.0-185.0 °C; yield 42%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.86 (dt, 1H, $J = 13.76$ Hz, 11.56 Hz, 5-CH(H)), 2.47 (ddd, 1H, $J = 13.76$ Hz, 4.40 Hz, 2.20 Hz, 1.65 Hz, 5-CH(H)), 3.46 (dd, 1H, $J = 10.73$ Hz, 6.88 Hz, CH(H)Br), 3.60 (dd, 1H, $J = 10.73$ Hz, 4.40 Hz, CH(H)Br), 4.57-4.65 (m, 1H, CHO), 4.63 (dd, 1H, $J = 11.70$ Hz, 4.5 Hz, CHN), 5.32 (br s, 1H, NH), 7.31-7.45 (m, 5H, C$_6$H$_5$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 32.6, 35.3, 55.2, 75.8, 126.2, 129.0, 129.3, 140.2, 153.1. IR (ATR, cm$^{-1}$): $\nu$ = 3222 (NH), 3116, 1694 (C=O). MS (ES, pos): $m/z$ 270/272 (M+H$^+$, 100). Anal. Calcd. for C$_{11}$H$_{12}$BrNO$_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.87; H, 4.09; N, 5.06.

4.2.4. *trans*-6-(Bromomethyl)-4-phenyl-1,3-oxazinan-2-one (10a). Isolated by column chromatography (diethyl ether). Amorphous white solid; mp: 157.1-159.1 °C; yield 14%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.17 (dd, 1H, $J = 13.9$ Hz, 3.9 Hz, 3.0 Hz, 1.1 Hz, 5-CH(H)), 2.40 (ddd, 1H, $J = 14.0$ Hz, 9.6 Hz, 5.8 Hz, 5-CH(H)), 3.48 (dd, 1H, $J = 10.8$ Hz, 6.7 Hz, CH(H)Br), 3.53 (dd, 1H, $J = 10.8$ Hz, 4.95 Hz, CH(H)Br), 4.42 (ddd, 1H, $J = 9.5$ Hz, 6.8 Hz, 4.9 Hz, 2.8 Hz, CHO), 4.79 (dt, 1H, $J = 5.5$ Hz, 3.6 Hz, CHN), 5.48 (br s, 1H, NH), 7.29-7.45 (m, 5H, C$_6$H$_5$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 32.3, 32.8, 52.3, 72.4, 125.9, 128.4, 129.2, 141.2, 153.2. IR (ATR, cm$^{-1}$): $\nu$ = 3243 (NH), 3124, 1690 (C=O). MS (ES, pos): $m/z$ 270/272 (M+H$^+$, 100). Anal. Calcd. for C$_{11}$H$_{12}$BrNO$_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.75; H, 4.29; N, 5.39.

4.2.5. *cis*-6-(Bromomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (10b). Isolated by column chromatography (diethyl ether). Colorless crystals; mp: 138.2-140.2 °C; yield 36%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.83 (dt, 1H, $J = 13.76$ Hz, 11.56 Hz, 5-CH(H)), 2.41 (ddd, 1H, $J = 13.7$ Hz, 4.2 Hz, 2.0 Hz, 2.0 Hz, 5-CH(H)), 3.46 (dd, 1H, $J = 10.73$ Hz, 6.88 Hz, CH(H)Br), 3.59 (dd, 1H, $J = 10.73$ Hz, 4.40 Hz, CH(H)Br), 3.82 (s, 3H, CH$_3$O), 4.54-4.62 (m, 1H, CHO), 4.57 (dd, 1H, $J = 11.56$ Hz, 4.68 Hz, CHN), 5.46 (br s, 1H, NH), 6.89-6.94 (m, 2H, Ar-H), 7.23-7.28 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 32.6, 35.4, 54.7, 55.5, 75.8, 114.6, 127.5, 132.1, 153.0, 160.0. IR (ATR, cm$^{-1}$): $\nu$ = 3222 (NH), 3116, 1694 (C=O). MS (ES, M+H$^+$, pos): $m/z$ 300/302 (M+H$^+$, 100). Anal. Calcd. for C$_{12}$H$_{14}$BrNO$_3$: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.34; H, 4.36; N, 4.55.
4.2.6. **trans-6-(Bromomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (10b).** Isolated by column chromatography (diethyl ether). White crystals; mp: 146.0-148.0 °C; yield 11%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.13$ (ddddd, 1H, $J = 14.0$ Hz, 4.1 Hz, 3.0 Hz, 1.0 Hz, 5-CH(H)), 2.36 (ddd, 1H, $J = 13.9$ Hz, 9.2 Hz, 5.6 Hz, 5-CH(H)), 3.48 (dd, 1H, $J = 10.7$ Hz, 6.9 Hz, CH(H)Br), 3.53 (dd, 1H, $J = 10.7$ Hz, 5.0 Hz, CH(H)Br), 3.82 (s, 3H, CH$_3$O), 4.43 (dddd, 1H, $J = 9.3$ Hz, 6.8 Hz, 4.8 Hz, 2.7 Hz, CHO), 4.74 (m, 1H, CHN), 5.41 (br s, 1H, NH), 6.90-6.95 (m, 2H, Ar-H), 7.21-7.24 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 32.2$, 32.9, 51.8, 55.5, 72.5, 114.5, 127.0, 133.1, 153.1, 159.6. IR (ATR, cm$^{-1}$): $\nu = 3242$ (NH), 3125, 1674 (C=O). MS (ES, M+H$^+$, pos): m/z 300/302 (M+H$^+$, 100). Anal. Calcd. for C$_{12}$H$_{14}$BrNO$_3$: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.40; H, 4.58; N, 4.58.

4.2.7. **cis-6-(Iodomethyl)-4-phenyl-1,3-oxazinan-2-one (10c).** Isolated by column chromatography (diethyl ether). Colorless crystals; mp: 181.5-183.5 °C; yield 31%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.80$ (dt, 1H, $J = 13.76$ Hz, 11.56 Hz, 5-CH(H)), 2.52 (ddt, 1H, $J = 13.76$ Hz, 4.40 Hz, 1.93 Hz, 5-CH(H)), 3.29 (dd, 1H, $J = 10.46$ Hz, 7.43 Hz, CH(H)I), 3.43 (dd, 1H, $J = 10.46$ Hz, 4.40 Hz, CH(H)I), 4.44 (ddddd, 1H, $J = 11.56$ Hz, 7.02 Hz, 4.54 Hz, 2.3 Hz, CHO), 4.63 (dd, 1H, $J = 11.56$ Hz, 4.68 Hz, CHN), 5.25 (br s, 1H, NH), 7.31-7.45 (m, 5H, C$_6$H$_5$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 5.5$, 36.9, 55.2, 76.1, 126.2, 129.0, 129.3, 140.2, 153.1. IR (ATR, cm$^{-1}$): $\nu = 3223$ (NH), 3121, 1696 (C=O). MS (ES, M+H$^+$, pos): m/z 318 (M+H$^+$, 100). Anal. Calcd. for C$_{11}$H$_{12}$INO$_2$: C, 41.66; H, 3.81; N, 4.42. Found: C, 41.52; H, 3.45; N, 4.29.

4.2.8. **trans-6-(Iodomethyl)-4-phenyl-1,3-oxazinan-2-one (10c).** Isolated by column chromatography (diethyl ether). Amorphous white solid; mp: 158.0-160.0 °C; yield 16%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.20$ (ddddd, 1H, $J = 13.9$ Hz, 4.0 Hz, 3.0 Hz, 1.0 Hz, 5-CH(H)), 2.37 (ddd, 1H, $J = 13.9$ Hz, 9.2 Hz, 5.8 Hz, 5-CH(H)), 3.31 (dd, 1H, $J = 10.73$ Hz, 6.88 Hz, CH(H)I), 3.36 (dd, 1H, $J = 10.73$ Hz, 4.95 Hz, CH(H)I), 4.24 (ddddd, 1H, $J = 9.2$ Hz, 7.1 Hz, 5.0 Hz, 3.0 Hz, CHO), 4.76 (dt, 1H, $J = 5.8$ Hz, 3.6 Hz, CHN), 5.40 (br s, 1H, NH), 7.30-7.45 (m, 5H, C$_6$H$_5$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 5.3$, 34.4, 52.3, 72.7, 125.8, 128.4, 129.2, 141.2, 153.2. IR (ATR, cm$^{-1}$): $\nu = 3322$ (NH), 1662 (C=O). MS (ES, M+H$^+$, pos): m/z 318 (M+H$^+$, 100). Anal. Calcd. for C$_{11}$H$_{12}$INO$_2$: C, 41.66; H, 3.81; N, 4.42. Found: C, 41.99; H, 3.50; N, 4.33.
4.2.9. *cis*-6-(Iodomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (10d). Isolated by column chromatography (diethyl ether). White amorphous solid; mp: 159.4-161.4 °C; yield 29%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.78$ (dt, 1H, $J = 14.03$ Hz, 11.4 Hz, 5-CH(H)), 2.47 (dddd, 1H, $J = 13.76$ Hz, 4.40 Hz, 2.0 Hz, 2.0 Hz, 5-CH(H)), 3.28 (dd, 1H, $J = 10.59$ Hz, 7.3 Hz, CH(H)I), 3.43 (dd, 1H, $J = 10.59$ Hz, 4.5 Hz, CH(H)I), 3.82 (s, 3H, CH$_3$O), 4.41 (dddd, 1H, $J = 11.28$ Hz, 7.1 Hz, 4.6 Hz, 2.0 Hz, CHO), 4.57 (dd, 1H, $J = 11.56$ Hz, 4.40 Hz, CHN), 5.31 (br s, 1H, NH), 6.89-6.94 (m, 2H, Ar-H), 7.23-7.28 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 5.7$, 37.0, 54.6, 55.5, 76.0, 114.6, 127.5, 132.1, 153.3, 160.0. IR (ATR, cm$^{-1}$): $\nu =$ 3249 (NH), 3113, 1682 (C=O). MS (ES, M+H$^+$, pos): m/z 348 (M+H$^+$, 100). Anal. Calcd. for C$_{12}$H$_{14}$INO$_3$: C, 41.52; H, 4.06; N, 4.03. Found: C, 41.56; H, 3.75; N, 4.01.

4.2.10. *trans*-6-(Iodomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (10d). Isolated by column chromatography (diethyl ether). Amorphous white solid; mp: 157.2-159.2 °C; yield 7%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.16$ (dddd, 1H, $J = 13.9$ Hz, 4.2 Hz, 3.1 Hz, 0.9 Hz, 5-CH(H)), 2.33 (ddd, 1H, $J = 14.1$ Hz, 8.9 Hz, 5.4 Hz, 5-CH(H)), 3.30 (dd, 1H, $J = 10.73$ Hz, 7.15 Hz, CH(H)I), 3.36 (dd, 1H, $J = 10.73$ Hz, 4.95 Hz, CH(H)I), 3.82 (s, 3H, CH$_3$O), 4.25 (dddd, 1H, $J = 9.1$ Hz, 7.15 Hz, 4.95 Hz, 3.03 Hz, CHO), 5.54 (br s, 1H, NH), 6.90-6.95 (m, 2H, Ar-H), 7.20-7.25 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 5.7$, 34.5, 51.7, 55.5, 72.8, 114.5, 127.0, 133.1, 153.3, 159.6. IR (ATR, cm$^{-1}$): $\nu =$ 3245 (NH), 1664 (C=O). MS (ES, M+H$^+$, pos): m/z 348 (M+H$^+$, 100). Anal. Calcd. for C$_{12}$H$_{14}$INO$_3$: C, 41.52; H, 4.06; N, 4.03. Found: C, 41.52; H, 3.70; N, 3.94.

4.2.11. 4-Phenyl-6-(phenylselanylmethyl)-1,3-oxazinan-2-one (10e). Mixture of *cis*- and *trans*-isomer in a ratio 54/46, crystallized from diethyl ether/hexane. Amorphous white solid; mp: 127.4-129.4 °C; yield 79%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.75$ (dt, 1H, $J = 13.76$ Hz, 11.56 Hz, 5-CH(H)$_{cis}$), 2.23-2.27 (m, 2H, 5-CH(H)$_{trans}$), 2.51 (ddt, 1H, $J = 13.76$ Hz, 4.68 Hz, 1.8 Hz, 5-CH(H)$_{cis}$), 2.95 (dd, 1H, $J = 12.80$ Hz, 9.2 Hz, CH(H)Se$_{trans}$), 2.98 (dd, 1H, $J = 12.93$ Hz, 8.53 Hz, CH(H)Se$_{cis}$), 3.24 (dd, 1H, $J = 12.93$ Hz, 4.68 Hz, CH(H)Se$_{trans}$), 3.33 (dd, 1H, $J = 12.93$ Hz, 4.68 Hz, CH(H)Se$_{cis}$), 4.24-4.34 (m, 1H, CHO$_{trans}$), 4.50 (dddd, 1H, $J = 11.39$ Hz, 8.6 Hz, 4.7 Hz, 2.0 Hz, CHO$_{cis}$), 4.56 (dd, 1H, $J = 11.42$ Hz, 4.5 Hz, CHN$_{cis}$), 4.64-4.68 (m, 1H, CHN$_{trans}$), 5.32 (br s, 1H, NH$_{cis}$), 5.60 (br s, 1H, NH$_{trans}$), 7.16-7.54 (m, 20H, Ar-H$_{cis+trans}$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 30.6$, 31.2, 33.4, 36.2, 52.6, 55.6, 73.5, 76.7 (overlap with signal from CDCl$_3$), 125.9, 126.2, 127.7, 127.9, 128.2, 128.8, 129.1, 129.3,
129.4, 129.5, 132.9, 134.0, 140.5, 141.5, 153.6, 153.7. IR (ATR, cm⁻¹): ν = 3211 (NH), 3109, 1686 (C=O). MS (ES, M+H⁺, pos): m/z 348/346 (M+H⁺, 100). Anal. Calcd. for C₁₇H₁₇NO₂Se: C, 58.96; H, 4.95; N, 4.04. Found: C, 59.08; H, 4.56; N, 4.02.

4.2.12. 4-(Methoxyphenyl)-6-(phenylselanylmethyl)-1,3-oxazinan-2-one (10f). Mixture of cis- and trans-isomer in a ratio 58/42, crystallized from diethyl ether/hexane. Amorphous white solid; mp: 93.1-95.1 °C; yield 85%. ¹H NMR (300 MHz, CDCl₃): δ = 1.74 (dt, 1H, J = 13.76 Hz, 11.56 Hz, 5-C(H)cis), 2.18-2.24 (m, 2H, 5-C(H)trans), 2.47 (ddt, 1H, J = 13.76 Hz, 4.40 Hz, 1.9 Hz, 5-C(H)cis), 2.97 (dd, 1H, J = 12.80 Hz, 9.2 Hz, CH(H)Setrans), 2.98 (dd, 1H, J = 13.07 Hz, 8.4 Hz, CH(H)Secis), 3.26 (dd, 1H, J = 12.80 Hz, 4.5 Hz, CH(H)Setrans), 3.33 (dd, 1H, J = 12.93 Hz, 4.68 Hz, CH(H)Secis), 3.81 (s, 3H, CH₃OCis), 3.82 (s, 3H, CH₃OTran), 4.27-4.35 (m, 1H, CHOtrans), 4.44-4.53 (m, 1H, CHOcis), 4.51 (dd, 1H, J = 11.28 Hz, 4.3 Hz, CHNcis), 4.57-4.62 (m, 1H, CHNtrans), 5.15 (br s, 1H, NHcis), 5.38 (br s, 1H, NHtrans), 6.86-7.54 (m, 18H, Ar-Hcis,trans). ¹³C NMR (75 MHz, CDCl₃): δ = 30.6, 31.3, 33.4, 36.3, 51.9, 55.0, 55.5, 73.6, 76.6, 114.3, 114.5, 127.1, 127.4, 127.6, 127.9, 128.6, 129.2, 129.4, 129.5, 132.4, 132.8, 133.5, 133.9, 153.8, 153.9, 159.4, 159.9. IR (ATR, cm⁻¹): ν = 3225 (NH), 3108, 1685 (C=O). MS (ES, M+H⁺, pos): m/z 378/376 (M+H⁺, 100). Anal. Calcd. for C₁₈H₁₉NO₃Se: C, 57.45; H, 5.09; N, 3.72. Found: C, 57.46; H, 5.10; N, 3.72.

4.2.13. Alternative procedure for the preparation of 4-aryl-1,3-oxazinan-2-ones 10. To a solution of homoallylamine 9 (1 mmol) in dichloromethane (20 mL) at 0 °C, TBDMSOTf (0.79 g, 3 mmol) and 2,6-lutidine (0.43 g, 4 mmol) was added. After stirring for 2 h at 0 °C, a solution of electrophile (2.44 mmol) in freshly distilled dry dichloromethane (10 mL) was added dropwise and the mixture was stirred at 0 °C under nitrogen atmosphere for 16 – 24 hours. After typical workup, the mixture was purified by column chromatography (EtOAc) to afford 4-aryl-1,3-oxazinan-2-ones 10 as a mixture of trans- and cis-isomers.

4.2.14. General procedure for the preparation of benzyl N-benzyl-N-(1-phenyl-3-butenyl)carbamates 11. Benzyl bromide (60 mmol) was added to a solution of sodium iodide in acetone (80 mL). The mixture was stirred for 24 h in the dark at room temperature, quenched with water (50 mL) and extracted with Et₂O (2 x 100 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the pure benzyl iodide as a yellow oil. Sodium hydride (5.25 mmol) was washed three times with n-pentane after which DMF (10 mL) was added. The suspension was cooled to 0 °C and a
solution of homoallylamine 9 (3.5 mmol) dissolved in dry DMF (8 mL) was added. The mixture was stirred for 30 min and then transferred by cannula into a flask containing benzyl iodide (60 mmol) in dry DMF (15 mL). The mixture was stirred for additional 10 min at room temperature. The reaction was quenched with saturated aqueous NH₄Cl solution and extracted with Et₂O (2 x 30 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/Et₂O 6:1) to give compounds 11.

4.2.15. Benzyl N-benzyl-N-(1-phenyl-3-butenyl)carbamate (11a). Colourless oil; yield 70%. ¹H NMR (300 MHz, CDCl₃, recorded at 50 °C): δ = 2.67 (t, 2H, J = 7.2 Hz, CH₂CH=), 4.19 (d, 1H, J = 15.69 Hz, NCH(H)), 4.42 (d, 1H, J = 15.69 Hz, NCH(H)), 4.93-4.99 (m, 2H, =CH₂), 5.17 (s, 2H, OCH₂), 5.32-5.43 (m, 1H, CH=N), 5.60-5.73 (m, 1H, CH=), 7.00-7.33 (m, 15H, Ar-H). IR (ATR, cm⁻¹): ν = 1691 (C=O). MS (ES, pos): m/z 372 (M+H⁺, 100). Purity >94% as determined by reverse phase HPLC analysis (integration at 220 nm).

4.2.16. Benzyl N-benzyl-N-(1-(4-methoxyphenyl)-3-butenyl)carbamate (11b). Colourless oil; yield 65%. ¹H NMR (300 MHz, CDCl₃, recorded at 50 °C): δ = 2.63 (t, 2H, J = 7.2 Hz, CH₂CH=), 3.78 (s, 3H, CH₃O), 4.16 (d, 1H, J = 15.96 Hz, NCH(H)), 4.40 (d, 1H, J = 15.69 Hz, NCH(H)), 4.92-4.98 (m, 2H, =CH₂), 5.17 (s, 2H, OCH₂), 5.28-5.38 (m, 1H, CHN), 5.59-5.72 (m, 1H, CH=), 6.77-6.82 (m, 2H, Ar-H), 7.00-7.32 (m, 12H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ = 36.1, 47.2 (broad), 55.4, 58.9, 67.4, 113.8, 117.5, 126.9, 127.3 (broad), 128.0 (broad), 128.2, 128.5, 129.6, 131.4, 135.0, 136.7, 139.1, 156.9, 159.1. IR (ATR, cm⁻¹): ν = 1691 (C=O), 1610. MS (ES, pos): m/z 402 (M+H⁺, 48), 294 (90), 250 (100), 204 (95), 161 (72). Purity >92% as determined by reverse phase HPLC analysis (integration at 220 nm).

4.2.17. General procedure for the preparation of 4-aryl-3-benzyl-1,3-oxazinan-2-ones 12. A solution of electrophile (1.22 mmol) in freshly distilled dry dichloromethane (10 mL) was added dropwise in a period of 10 minutes to a stirred solution of benzyl N-benzyl-N-(1-phenyl-3-butenyl)carbamate 11 (1.0 mmol) in dichloromethane (20 mL) and the mixture was stirred at room temperature under nitrogen atmosphere for 18 – 40 hours. After typical workup, the mixture was purified by column chromatography (EtOAc) to afford 4-aryl-3-benzyl-1,3-oxazinan-2-ones 12 as a mixture of trans- and cis-isomers.
4.2.18. **trans-3-Benzyl-6-(bromomethyl)-4-phenyl-1,3-oxazinan-2-one (12a).** Isolated by column chromatography (EtOAc) and crystallization from dichloromethane/hexane. Amorphous white solid; mp: 131.7-133.7 °C; yield 86%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 2.13 (ddd, 1H, $J = 13.76$ Hz, 2.75 Hz, 2.75 Hz, 5-CH(H)), 2.20 (ddd, 1H, $J = 13.69$ Hz, 10.9 Hz, 5.6 Hz, 5-CH(H)), 3.42 (dd, 1H, $J = 10.87$ Hz, 6.2 Hz, CH(H)Br), 3.47 (dd, 1H, $J = 10.87$ Hz, 4.5 Hz, CH(H)Br), 3.66 (d, 1H, $J = 15.13$ Hz, NCH(H)), 4.36-4.44 (m, 1H, CHO), 4.53 (dd, 1H, $J = 5.50$ Hz, 2.48 Hz, CHN), 5.40 (d, 1H, $J = 15.13$ Hz, NCH(H)), 7.20-7.47 (m, 10H, 2xC$_6$H$_5$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 33.0, 34.2, 50.5, 55.8, 71.6, 126.3, 128.0, 128.3, 128.4, 128.9, 136.5, 139.5, 153.6. IR (ATR, cm$^{-1}$): $\nu =$ 1674 (C=O). MS (ES, pos): m/z 360/362 (M+H+, 100). Anal. Calcd. for C$_{18}$H$_{18}$BrNO$_2$: C, 60.01; H, 5.04; N, 3.89. Found: C, 59.94; H, 4.64; N, 3.83.

4.2.19. **trans-3-Benzyl-6-(bromomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (12b).** Isolated together with the cis-isomer 12b as 85:15 mixture by column chromatography (EtOAc). Viscous colourless oil; yield 85%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 2.09 (ddd, 1H, $J = 13.7$ Hz, 2.8 Hz, 2.8 Hz, 5-CH(H)), 2.16 (ddd, 1H, $J = 13.7$ Hz, 11.01 Hz, 5.6 Hz, 5-CH(H)), 3.41 (dd, 1H, $J = 10.8$ Hz, 6.33 Hz, CH(H)Br), 3.47 (dd, 1H, $J = 10.8$ Hz, 4.68 Hz, CH(H)Br), 3.84 (s, 3H, CH$_3$O), 3.65 (d, 1H, $J = 15.13$ Hz, NCH(H)), 4.37-4.45 (m, 1H, CHO), 4.47 (dd, 1H, $J = 5.23$ Hz, 2.20 Hz, CHN), 5.37 (d, 1H, $J = 15.13$ Hz, NCH(H)), 6.92-7.37 (m, 9H, Ar-H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 33.0, 34.3, 50.5, 55.3, 55.5, 71.7, 114.7, 127.5, 127.9, 128.3, 128.9, 131.3, 136.5, 153.6, 159.6. IR (ATR, cm$^{-1}$): $\nu =$ 1689 (C=O). MS (ES, pos): m/z 390/392 (M+H$^+$, 100). Anal. Calcd. for C$_{18}$H$_{15}$BrNO$_2$: C, 60.01; H, 5.04; N, 3.89. Found: C, 59.94; H, 4.64; N, 3.83.

4.2.20. **trans-3-Benzyl-6-(iodomethyl)-4-phenyl-1,3-oxazinan-2-one (12c).** Isolated together with the cis-isomer 12c as 94:6 mixture by column chromatography (EtOAc) and crystallization from dichloromethane/hexane. Amorphous white solid; mp: 135.8-137.8 °C; yield 85%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 2.07-2.21 (m, 2H, 5-CH$_2$), 3.23 (dd, 1H, $J =$ 10.59 Hz, 6.5 Hz, CH(H)I), 3.30 (dd, 1H, $J =$ 10.59 Hz, 4.8 Hz, CH(H)I), 3.65 (d, 1H, $J =$ 15.13 Hz, NCH(H)), 4.14-4.22 (m, 1H, CHO), 4.51 (dd, 1H, $J =$ 5.23 Hz, 2.75 Hz, CHN), 5.40 (d, 1H, $J =$ 15.13 Hz, NCH(H)), 7.18-7.46 (m, 10H, 2xC$_6$H$_5$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 6.3, 35.9, 50.5, 55.8, 71.8, 126.3, 127.9, 128.3, 128.4, 128.9, 129.4, 136.5, 139.6,
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IR (ATR, cm\(^{-1}\)): \(\nu = 1677\) (C=O). MS (ES, pos): m/z 408 (M+H\(^+\), 100). Anal. Calcd. for C\(_{18}\)H\(_{18}\)INO\(_2\): C, 53.09; H, 4.46; N, 3.44. Found: C, 52.73; H, 4.16; N, 3.62.

4.2.21. \textit{trans}-3-Benzyl-6-(iodomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (12d).

Isolated together with the \textit{cis}-isomer 12d as 91:9 mixture by column chromatography (EtOAc). Viscous yellow oil; yield 86%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.04-2.18\) (m, 2H, 5-CH\(_2\)), 3.23 (dd, 1H, \(J = 10.46\) Hz, 6.60 Hz, CH(H)I), 3.30 (dd, 1H, \(J = 10.46\) Hz, 4.68 Hz, CH(H)I), 3.65 (d, 1H, \(J = 14.86\) Hz, NCH(H)), 3.84 (s, 3H, CH\(_3\)O), 4.15-4.23 (m, 1H, CHO), 4.45 (dd, 1H, \(J = 4.95\) Hz, 2.75 Hz, CHN), 5.38 (d, 1H, \(J = 15.13\) Hz, NCH(H)), 6.92-7.37 (m, 9H, Ar-H). IR (ATR, cm\(^{-1}\)): \(\nu = 1687\) (C=O). MS (ES, pos): m/z 438 (M+H\(^+\), 100). Anal. Calcd. for C\(_{19}\)H\(_{20}\)INO\(_3\): C, 52.19; H, 4.61; N, 3.20. Found: C, 52.53; H, 4.83; N, 3.44.

4.2.22. 3-Benzyl-6-(phenylselanylmethyl)-4-phenyl-1,3-oxazinan-2-one (12e).

Isolated as a 66:33 \textit{trans}/\textit{cis} mixture by column chromatography (EtOAc). Viscous colourless oil; yield 78%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.93\) (dt, 1H, \(J = 14.03\) Hz, 11.4 Hz, 5-C\(_{\text{cis}}\)H\(_{\text{cis}}\)), 2.06 (ddd, 1H, \(J = 13.76\) Hz, 10.7 Hz, 5.8 Hz, 5-CH(H)\(_{\text{trans}}\)), 2.27 (dt, 1H, \(J = 13.76\) Hz, 2.48 Hz, 5-CH(H)\(_{\text{trans}}\)), 2.52 (ddd, 1H, \(J = 13.97\) Hz, 1.9 Hz, 5-CH(H)\(_{\text{cis}}\)), 2.85 (dd, 1H, \(J = 12.66\) Hz, 8.81 Hz, CH(H)Se\(_{\text{trans}}\)), 2.94 (dd, 1H, \(J = 12.93\) Hz, 8.26 Hz, CH(H)Se\(_{\text{cis}}\)), 3.20 (dd, 1H, \(J = 12.93\) Hz, 4.40 Hz, CH(H)Se\(_{\text{trans}}\)), 3.30 (dd, 1H, \(J = 12.93\) Hz, 4.68 Hz, CH(H)Se\(_{\text{cis}}\)), 3.54 (d, 1H, \(J = 15.13\) Hz, NCH(H)\(_{\text{cis}}\)), 3.60 (d, 1H, \(J = 15.13\) Hz, NCH(H)\(_{\text{trans}}\)), 4.22-4.38 (m, 3H, CHO\(_{\text{trans}}\) and CHN\(_{\text{cis}}\)), 4.43 (dd, 1H, \(J = 5.78\) Hz, 2.20 Hz, CHN\(_{\text{trans}}\)), 5.22 (d, 1H, \(J = 14.86\) Hz, NCH(H)\(_{\text{cis}}\)), 5.36 (d, 1H, \(J = 15.13\) Hz, NCH(H)\(_{\text{trans}}\)), 7.03-7.51 (m, 30H, Ar-H\(_{\text{cis+trans}}\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 31.0, 31.1, 34.8, 38.0, 48.9, 50.4, 56.1, 58.6, 72.6, 74.9, 126.4, 127.1, 127.6, 127.7, 127.8, 128.1, 128.3, 128.5, 128.6, 128.7, 128.8, 129.2, 129.3, 129.5, 132.8, 134.1, 136.7, 136.8, 139.8, 139.9, 154.2, 154.8. IR (ATR, cm\(^{-1}\)): \(\nu = 1688\) (C=O). MS (ES, pos): m/z 436/438 (M+H\(^+\), 100). Anal. Calcd. for C\(_{24}\)H\(_{23}\)NO\(_2\)Se: C, 66.05; H, 5.31; N, 3.21. Found: C, 65.67; H, 5.58; N, 3.52.

4.2.23. 3-Benzyl-4-(4-methoxyphenyl)-6-(phenylselanylmethyl)-1,3-oxazinan-2-one (12f).

Isolated as a 50:50 \textit{trans}/\textit{cis} mixture by column chromatography (EtOAc). Viscous yellow oil; yield 82%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.92\) (dt, 1H, \(J = 14.31\) Hz, 11.5 Hz, 5-CH(H)\(_{\text{cis}}\)),
2.02 (ddd, 1H, \( J = 13.62 \text{ Hz}, 10.87 \text{ Hz}, 5.6 \text{ Hz} \)), 5-CH(\text{H})_{\text{trans}}, 2.22 (dt, 1H, \( J = 13.48 \text{ Hz}, 2.48 \text{ Hz} \)), 5-CH(\text{H})_{\text{cis}}, 2.49 (ddd, 1H, \( J = 13.97 \text{ Hz}, 1.6 \text{ Hz} \)), 5-CH(\text{H})_{\text{trans}}, 2.85 (dd, 1H, \( J = 12.80 \text{ Hz}, 8.9 \text{ Hz} \)), 5-CH(\text{H})_{\text{cis}}, 2.95 (dd, 1H, \( J = 12.93 \text{ Hz}, 8.53 \text{ Hz} \)), 5-CH(\text{H})_{\text{cis}}, 3.21 (dd, 1H, \( J = 13.97 \text{ Hz}, 6.1 \text{ Hz} \)), 5-CH(\text{H})_{\text{trans}}, 3.30 (ddd, 1H, \( J = 13.48 \text{ Hz}, 2.48 \text{ Hz} \)), 5-CH(\text{H})_{\text{cis}}, 3.55 (d, 1H, \( J = 15.13 \text{ Hz} \)), 3.60 (d, 1H, \( J = 15.13 \text{ Hz} \)), 3.83 (s, 3H, \( \text{CH}_3 \text{O} \)), 3.85 (s, 3H, \( \text{CH}_3 \text{O} \)), 4.21-4.34 (m, 3H, \( \text{CHO} \)), 4.37 (dd, 1H, \( J = 5.50 \text{ Hz}, 2.75 \text{ Hz} \)), 5.19 (d, 1H, \( J = 15.13 \text{ Hz} \)), 5.34 (d, 1H, \( J = 15.13 \text{ Hz} \)), 6.88-7.51 (m, 28H, \( \text{Ar -H} \)).

13C NMR (75 MHz, CDCl3): \( \delta = 31.1 \) (2C), 34.9, 38.0, 48.7, 50.3, 55.5 (2C), 55.6, 58.1, 72.6, 74.9, 114.5, 127.5, 127.6, 127.77, 127.85, 128.3, 128.4, 128.7, 128.8, 129.3, 129.4, 131.6, 131.8, 132.8, 134.0, 136.8, 136.9, 154.2, 154.8, 159.4, 159.7. IR (ATR, cm\(^{-1}\)): \( \nu = 1687 \) (C=O). MS (ES, pos): \( m/z \) 466/468 (M+H\(^+\), 100). Anal. Calcd. for C\(_{25}\)H\(_{25}\)NO\(_3\)Se: C, 64.38; H, 5.40; N, 3.00. Found: C, 64.70; H, 5.69; N, 3.38.

4.2.24. General procedure for the synthesis of 6-arylpiperidine-2,4-diones 15. To a solution of 4-aryl-6-(iodomethyl)-1,3-oxazinan-2-one 10 (1 mmol) in ethanol (25 mL) was added a 5 M aqueous solution of NaOH (25 mL) and the reaction mixture was stirred under reflux for 8 h. After completion of the reaction, 5% HCl (aq.) was added and the reaction mixture was extracted with EtOAc and CH\(_2\)Cl\(_2\). The combined organic layers were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The residue was crystallized from CH\(_2\)Cl\(_2\)/hexane to afford the pure 6-arylpiperidine-2,4-diones 15.

4.2.25. 6-Phenylpiperidine-2,4-dione 15a. Amorphous yellowish solid; mp: 166.2-168.2 °C (lit. mp: 167-169 °C, \( \text{C}^{27} \) 166-168 °C for (R)-(+)\text{-}15a\textsuperscript{29}, 164-168 °C\textsuperscript{32}); yield 86%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.77 \) (dd, 1H, \( J = 16.0 \text{ Hz}, 9.5 \text{ Hz} \)), 2.90 (dd, 1H, \( J = 16.0 \text{ Hz} \)), 4.40 Hz, 5-CH(\text{H}), 3.39 (s, 2H, 3-CH\(_2\)), 4.82 (ddd, 1H, \( J = 9.56 \text{ Hz}, 4.5 \text{ Hz}, 1.7 \text{ Hz} \), CH\(_2\)), 6.25 (br s, 1H, NH), 7.31-7.47 (m, 5H, \( \text{C}6\text{H}_5\)). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 47.1, 47.3, 52.9, 126.1, 128.9, 129.5, 139.3, 169.3, 202.4. \) IR (ATR, cm\(^{-1}\)): \( \nu = 3185 \) (NH), 1715 (C=O), 1667 (NC=O). MS (ES, pos): \( m/z \) 190 (M+H\(^+\), 100). All spectroscopic data are in good correspondence with reported data.\textsuperscript{27,29,32}

4.2.26. 6-(4-Methoxyphenyl)piperidine-2,4-dione 15b. Amorphous white solid; mp: 172.4-174.4 °C (lit. mp: 174-175 °C, \( \text{C}^{27} \) 171-172 °C\textsuperscript{43}); yield 82%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.77 \) (dd, 1H, \( J = 16.0 \text{ Hz}, 9.5 \text{ Hz} \)), 2.90 (dd, 1H, \( J = 16.0 \text{ Hz} \)), 4.40 Hz, 5-CH(\text{H}), 3.39 (s, 2H, 3-CH\(_2\)), 4.82 (ddd, 1H, \( J = 9.56 \text{ Hz}, 4.5 \text{ Hz}, 1.7 \text{ Hz} \), CH\(_2\)), 6.25 (br s, 1H, NH), 7.31-7.47 (m, 5H, \( \text{C}_6\text{H}_5\)). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 47.1, 47.3, 52.9, 126.1, 128.9, 129.5, 139.3, 169.3, 202.4. \) IR (ATR, cm\(^{-1}\)): \( \nu = 3185 \) (NH), 1715 (C=O), 1667 (NC=O). MS (ES, pos): \( m/z \) 190 (M+H\(^+\), 100). All spectroscopic data are in good correspondence with reported data.\textsuperscript{27,29,32}
2.74 (dd, 1H, J = 16.1 Hz, 9.36 Hz, 5-CH(H)), 2.85 (dd, 1H, J = 16.1 Hz, 4.40 Hz, 5-CH(H)), 3.36 (s, 2H, 3-CH2), 3.82 (s, 3H, OCH3), 4.76 (dd, 1H, J = 9.36 Hz, 4.40 Hz, CH), 6.37 (br s, 1H, NH), 6.93 (d, 2H, J = 8.81 Hz, Ar-H), 7.24 (d, 2H, J = 8.81 Hz, Ar-H). 13C NMR (75 MHz, CDCl3): δ = 47.29, 47.33, 52.5, 55.5, 114.8, 127.4, 131.1, 160.0, 168.8, 202.5. IR (ATR, cm⁻¹): ν = 3183 (NH), 1722 (C=O), 1665 (NC=O). MS (ES, pos): m/z 220 (M+H⁺, 100).

4.2.27. General procedure for the preparation of 6-(azidomethyl)-1,3-oxazinan-2-ones 17.
To a solution of 6-(iodomethyl)-1,3-oxazinan-2-one 10 (1 mmol) in DMSO (10 mL) was added sodium azide (2 mmol) and the reaction mixture was stirred at 80 °C for 14 h. After cooling, the reaction mixture was poured into H2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine. The organic layer was dried (MgSO4), filtered and evaporated under reduced pressure. Crystallisation of the residue from CH2Cl2/hexane afforded the pure 6-(azidomethyl)-1,3-oxazinan-2-ones 17 in 81-85% yield.

4.2.28. 6-(Azidomethyl)-4-phenyl-1,3-oxazinan-2-one (17a).
Mixture of cis- and trans-isomer in a ratio 69/31. Amorphous purple solid; mp: 122.7-125.7 °C; yield 81%. 1H NMR (300 MHz, CDCl3): δ = 1.91 (dt, 1H, J = 13.76 Hz, 11.83 Hz, 5-CH(H)cis), 1.93-2.01 (m, 1H, 5-CH(H)trans), 2.17-2.24 (m, 1H, 5-CH(H)cis), 3.43 (dd, 1H, J = 13.07 Hz, 5.1 Hz, CH(N3)cis), 3.49-3.56 (m, 3H, CH(N3)cis and CH(N3)trans), 4.31-4.38 (m, 1H, CHOtrans), 4.55 (dddd, 1H, J = 11.70 Hz, 5.0 Hz, 5.0 Hz, 2.1 Hz, CHOcis), 4.62 (dd, 1H, J = 11.56 Hz, 4.40 Hz, CHNcis), 4.82 (dt, 1H, J = 5.8 Hz, 3.0 Hz, CHNtrans), 5.26 (br s, 1H, NHcis), 5.58 (br s, 1H, NHtrans), 7.29-7.44 (m, 10H, 2xC6H5). 13C NMR (75 MHz, CDCl3): δ = 31.7, 33.9, 52.4, 53.6, 53.8, 55.3, 71.9, 75.4, 125.8, 126.0, 128.2, 128.9, 129.1, 129.3, 140.1, 141.3, 153.0, 153.2. IR (ATR, cm⁻¹): ν = 3239 (NH), 3123, 2098 (N 3), 1696 (C=O). MS (ES, pos): m/z 233 (M+H⁺, 100). Purity >96% as determined by reverse phase HPLC analysis (integration at 220 nm).

4.2.29. 6-(Azidomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (17b).
Mixture of cis- and trans-isomer in a ratio 82/18. Amorphous grey solid; mp: 158.1-160.1 °C; yield 85%. 1H NMR (300 MHz, CDCl3): δ = 1.88 (dt, 1H, J = 13.76 Hz, 11.7 Hz, 5-CH(H)cis), 1.89-1.96 (m, 1H, 5-CH(H)trans), 2.11-2.19 (m, 1H, 5-CH(H)cis), 2.30 (dd, 1H, J = 13.9 Hz, 10.3 Hz, 5.9 Hz, 5-CH(H)trans), 3.43 (dd, 1H, J = 12.93 Hz, 5.23 Hz, CH(H)N3trans), 3.47-3.53 (m, 1H, CH(H)N3trans), 3.53 (dd, 1H, J = 13.21 Hz, 4.95 Hz, CH(H)N3cis), 3.54 (dd, 1H, J = 13.21 Hz,
4.95 Hz, CH(H)N$_3$, cis), 3.81 (s, 3H, CH$_3$O, trans), 3.82 (s, 3H, CH$_3$O, cis), 4.33 (ddddd, 1H, $J = 10.25$ Hz, 5.0 Hz, 5.0 Hz, 2.7 Hz, CH$_2$(trans), 4.48-4.56 (m, 1H, CH$_2$(cis), 4.56 (dd, 1H, $J = 11.42$ Hz, 4.5 Hz, CHN, cis), 4.76 (dt, 1H, $J = 5.5$ Hz, 3.2 Hz, CHN(trans), 5.47 (br s, 1H, NH, cis), 5.94 (br s, 1H, NH, trans), 6.89-6.94 (m, 4H, Ar-H), 7.20-7.27 (m, 4H, Ar-H). $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$): $\delta = 31.8, 33.9, 51.8, 53.6, 53.8, 54.7, 55.4, 71.9, 75.4, 114.3, 114.5, 126.9, 127.4, 132.0, 133.2, 153.0, 153.3, 159.4, 159.9. IR (ATR, cm$^{-1}$): $\nu = 3325$ (NH), 2138 (N$_3$), 2110 (N$_3$), 1711 (C=O). MS (ES, pos): $m/z$ 263 (M+H$^+$, 100). Purity >95% as determined by reverse phase HPLC analysis (integration at 220 nm).

4.2.30. General procedure for the synthesis of 4-amino-4-aryl-1-azidobutan-2-ols 18. To a solution of 6-(azidomethyl)-1,3-oxazinan-2-one 17 (1 mmol) in MeOH (10 mL) was added 2 M NaOMe in MeOH (2 mL, 4 mmol). The solution was stirred under reflux for 48 h, evaporated under reduced pressure, diluted with CH$_2$Cl$_2$ (50 mL) and H$_2$O (50 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered and evaporated under reduced pressure. Purification by column chromatography with EtOAc afforded the pure aminoalcohol 18 in 81-90% yield.

4.2.31. 4-Amino-1-azido-4-phenylbutan-2-ol 18a. Mixture of syn- and anti-isomer in a ratio 78/22. Amorphous yellowish solid; mp: 52.5-55.2 °C; yield 90%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.73-1.84$ (m, 3H, 3-CH$_3$(H)$_{syn}$ and 3-CH$_3$(H)$_{anti}$), 1.93 (ddd, 1H, $J = 14.31$ Hz, 8.67 Hz, 3.7 Hz, 3-CH$_3$(H)$_{anti}$), 3.22-3.34 (m, 4H, CH($H$)$_3$N$_3$, anti+syn), 3.91 (ddt, 1H, $J = 8.53$ Hz, 5.4 Hz, 3.03 Hz, CHO$_{anti}$), 4.02-4.07 (m, 1H, CHN$_{syn}$), 4.10-4.17 (m, 1H, CHO$_{syn}$), 4.46 (dd, 1H, $J = 6.60$ Hz, 3.58 Hz, CH$_N_{anti}$), 7.23-7.40 (m, 10H, Ar-H$_{anti+syn}$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 40.3, 40.6, 53.7, 56.7, 56.9 (2C), 68.7, 71.1, 125.4, 125.9, 127.51, 127.54, 128.9, 129.1, 144.2, 146.4. IR (ATR, cm$^{-1}$): $\nu = 3356$ (OH), 3288 (NH), 2095 (N$_3$). MS (ES, pos): $m/z$ 207 (M+H$^+$, 100). Purity >92% as determined by reverse phase HPLC analysis (integration at 220 nm).

4.2.32. syn-4-Amino-1-azido-4-(4-methoxyphenyl)butan-2-ol 18b. Isolated in a syn/anti ratio >90/10. Amorphous yellowish solid; mp: 63.1-65.8 °C; yield 81%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.72-1.85$ (m, 2H, 3-CH(H)$_{H}$), 3.25 (dd, 1H, $J = 12.38$ Hz, 5.78 Hz, CH(H)N$_3$), 3.30 (dd, 1H, $J = 12.66$ Hz, 5.0 Hz, CH(H)N$_3$), 3.81 (s, 3H, CH$_3$O), 4.98-4.03 (m, 1H, CHN), 4.07-4.15 (m, 1H, CHO), 4.46 (dd, 1H, $J = 6.60$ Hz, 3.58 Hz, CHN$_{anti}$), 6.87-6.90 (m, 2H, Ar-
H), 7.15-7.19 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 40.5, 55.3, 56.1, 56.8, 71.9, 114.2, 126.4, 138.6, 158.8. IR (ATR, cm$^{-1}$): $\nu$ = 3366 (OH), 3293 (NH), 2097 (N$_3$). MS (ES, pos): m/z no M+H$^+$, 192 (100). Purity >87% as determined by reverse phase HPLC analysis (integration at 220 nm).

### 4.2.33. General procedure for the synthesis of 4-amino-4-aryl-1-(phenylselanyl)butan-2-ols 19.

To a solution of 6-(phenylselanylmethyl)-1,3-oxazinan-2-one 10 (1 mmol) in MeOH (10 mL) was added 2 M NaOMe in MeOH (2 mL, 4 mmol). The solution was stirred under reflux for 36-40 h, evaporated under reduced pressure, diluted with CH$_2$Cl$_2$ (50 mL) and H$_2$O (50 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered and evaporated under reduced pressure. Purification by column chromatography with EtOAc afforded the pure aminoalcohol 19 in 80-84% yield.

### 4.2.34. 4-Amino-4-phenyl-1-(phenylselanyl)butan-2-ol 19a.

Mixture of syn- and anti-isomer in a ratio 2/3. Amorphous white solid; mp: 95.7-97.7 °C; yield 84%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.75 (dt, 1H, $J$ = 14.03 Hz, 10.46 Hz, 3-CH$_2$(H)$_{\text{anti}}$), 1.90-2.02 (m, 3H, 3-CH(H)$_{\text{syn}}$ and 3-CH(H)$_{\text{anti}}$), 2.82-3.33 (m, 8H, CH(H)Se$_{\text{anti+syn}}$ and NH$_2$$_{\text{anti+syn}}$), 3.87-3.95 (m, 1H, CHO$_{\text{syn}}$), 4.01 (dd, 1H, $J$ = 10.73 Hz, 2.75 Hz, CHN$_{\text{anti}}$), 4.04-4.12 (m, 1H, CHO$_{\text{anti}}$), 4.33 (t, 1H, $J$ = 5.6 Hz, CHN$_{\text{syn}}$), 7.19-7.53 (m, 20H, Ar-H$_{\text{anti+syn}}$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 35.7, 35.9, 43.0, 43.3, 53.4, 56.7, 68.4, 71.9, 125.6, 126.0, 126.9, 127.1, 127.3, 127.4, 128.8, 129.0, 129.2, 130.0, 130.6, 132.5, 133.0, 145.1, 146.6. IR (ATR, cm$^{-1}$): $\nu$ = 3342 (OH), 3273 (NH). MS (ES, M+H$^+$, pos): m/z 322/320 (M+H$^+$, 100). Anal. Calcd. for C$_{16}$H$_{19}$NOSe: C, 60.00; H, 5.98; N, 4.37. Found: C, 60.36; H, 5.69; N, 4.37.

### 4.2.35. 4-Amino-4-(methoxyphenyl)-1-(phenylselanyl)butan-2-ol 19b.

Mixture of syn- and anti-isomer in a ratio 49/51. Amorphous white solid; mp: 101.3-103.3 °C; yield 80%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.73 (dt, 1H, $J$ = 14.03 Hz, 10.46 Hz, 3-CH(H)$_{\text{anti}}$), 1.88-1.99 (m, 3H, 3-CH(H)$_{\text{syn}}$ and 3-CH(H)$_{\text{anti}}$), 2.95-3.11 (m, 4H, CH(H)Se$_{\text{anti+syn}}$), 3.80 (s, 3H, CH$_3$O$_{\text{syn}}$), 3.81 (s, 3H, CH$_3$O$_{\text{anti}}$), 3.86-3.947 (m, 1H, CHO$_{\text{syn}}$), 3.97 (dd, 1H, $J$ = 10.73 Hz, 3.03 Hz, CHN$_{\text{anti}}$), 4.03-4.11 (m, 1H, CHO$_{\text{anti}}$), 4.30 (t, 1H, $J$ = 5.6 Hz, CHN$_{\text{syn}}$), 6.85-7.53 (m, 18H, Ar-H$_{\text{anti+syn}}$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 35.7, 35.9, 43.0, 43.4, 52.9, 55.4, 56.1, 68.4, 71.8, 114.1, 114.2, 126.6, 126.9, 127.0, 127.1, 129.2, 130.0, 130.6, 132.5, 133.0, 137.1, 139.0, 158.8. IR (ATR, cm$^{-1}$): $\nu$ = 3338 (OH), 3259 (NH). MS (ES, M+H$^+$, pos): m/z 333/335
(100). Anal. Calcd. for C₁₇H₂₁NO₂Se: C, 58.29; H, 6.04; N, 4.00. Found: C, 57.97; H, 6.36; N, 4.15.

4.3. Crystal Data. Compound cis-10b was crystallized (colorless blocks) by slow evaporation from a diethyl ether solution at room temperature. C₁₂H₁₄BrNO₃, Mr = 300.15, monoclinic, space group P₂₁/c, a = 14.6488(9) Å , b = 6.2920(4) Å , c = 15.2272(7) Å , U = 1275.36(13) Å³, Z = 4, T = 173(2) K, 9756 reflections measured, 2290 unique (Rint = 0.057). The final wR(F²) was 0.088 (all data). Crystallographic data for the structural analysis of compound cis-10b have been deposited at the Cambridge Crystallographic Data Centre. The CCDC 767171 has been assigned to the compound cis-10b. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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