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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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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 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 products[6] or biologically relevant compounds,[7] and are naturally occurring compounds, e.g., the maytansinoid antitumour 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 dihydrotetrabenazine (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.

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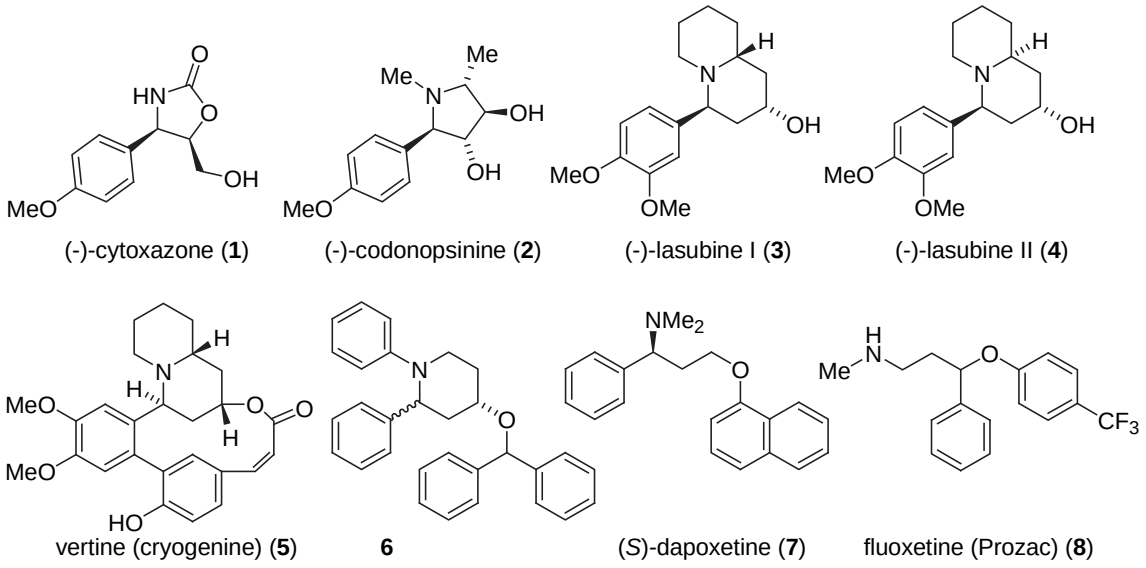
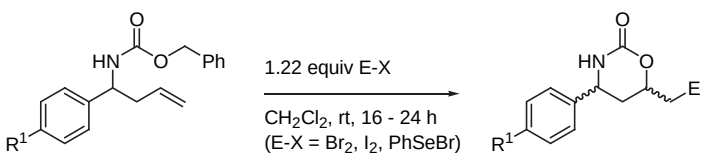


2. Results and discussion

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,[6a,d–f,h,10b,22] 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.[6a,d,h,10b,22a,b] Moreover, a lack of diastereoselectivity in some cyclocarbamations detracts from synthetic utility.[6d,22c,d] 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,[23] 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,[24] 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 CH_2Br to CH_2SePh. 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 ($^3J_{H-H}$) of H4, H5, H5′ and H6 (Fig. 1). The 6-substituent occupies an equatorial position both in the *cis*- and *trans*-isomers **10** as demonstrated by the typical large coupling constants $^3J_{H6-H5}$=9.0–11.6 Hz for the axial protons H5 and H6.[10b,22a] For the *cis*-isomers **10**, a large coupling constant $^3J_{H4-H5}$=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 (Fig. 2).

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 h and the yield dropped to 74% after extractive work up with 2 M 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-4*H*-[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



9a (R^1 = H)
9b (R^1 = OMe)

10a (R^1 = H, E = Br, 83%, dr *cis*/*trans* 75:25)
10b (R^1 = OMe, E = Br, 86%, dr *cis*/*trans* 80:20)
10c (R^1 = H, E = I, 84%, dr *cis*/*trans* 74:26)
10d (R^1 = OMe, E = I, 90%, dr *cis*/*trans* 78:22)
10e (R^1 = H, E = SePh, 79%, dr *cis*/*trans* 54:46)
10f (R^1 = OMe, E = SePh, 85%, dr *cis*/*trans* 58:42)

Scheme 1.

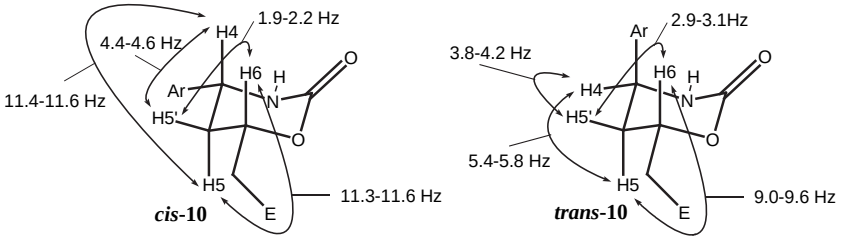


Figure 1. Selected coupling constants for *cis*- and *trans*-oxazinanones **10**.

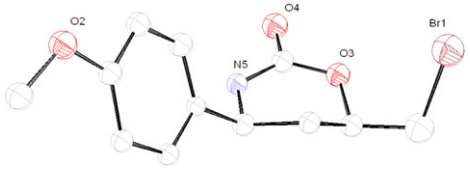
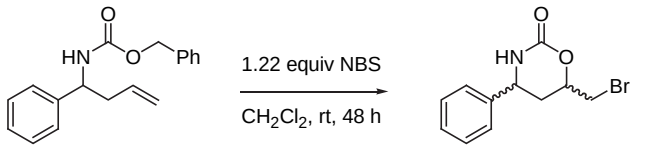


Figure 2. Ortep view of compound *cis*-**10b** by X-ray diffraction analysis.

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.



9a **10a** (74%, dr *cis*/*trans* 9:1)

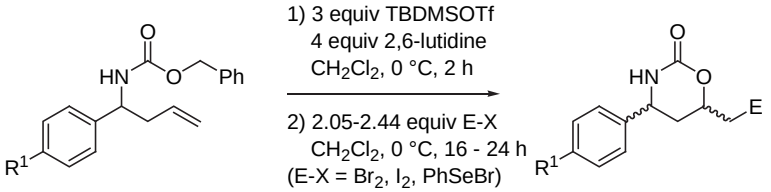
Scheme 2.

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.[6a] Treatment of the homoallylamines **9** with TBDMS triflate in the presence of 2,6-lutidine in dichloromethane at 0 °C for 2 h, followed by reaction with excess of bromine, iodine or phenylselenyl bromide at 0 °C for 16–24 h 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-butenyl)carbamates **9b**, the typical excess of 2.44 equiv of electrophile was lowered to 2.05 equiv of Br_2 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**.

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).[6a] 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).

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 (Fig. 3).[6d] 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.

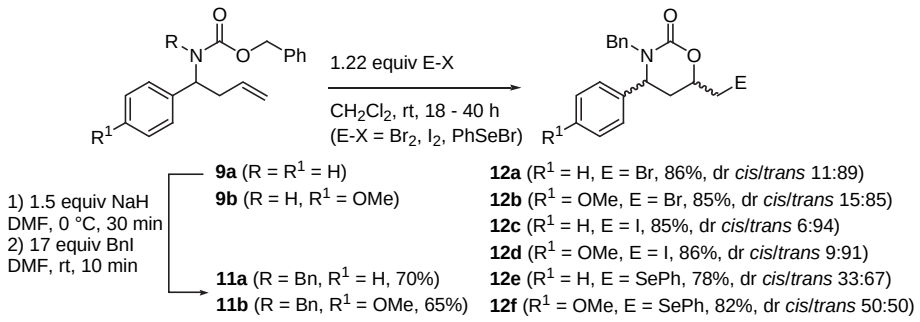
Having the functionalized 1,3-oxazinan-2-ones **10** in hand, their synthetic potential was studied under different conditions. A typical attempt to hydrolyze the 6-(iodomethyl)-1,3-oxazinan-2-ones **10c**,**d** directly to the corresponding 1,3-aminoalcohols,[10a] afforded an unexpected but interesting 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,[26]



9a (R^1 = H)
9b (R^1 = OMe)

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

Scheme 3.



Scheme 4.

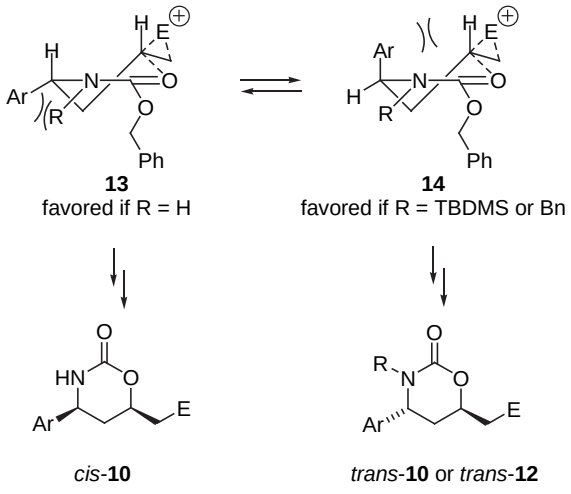
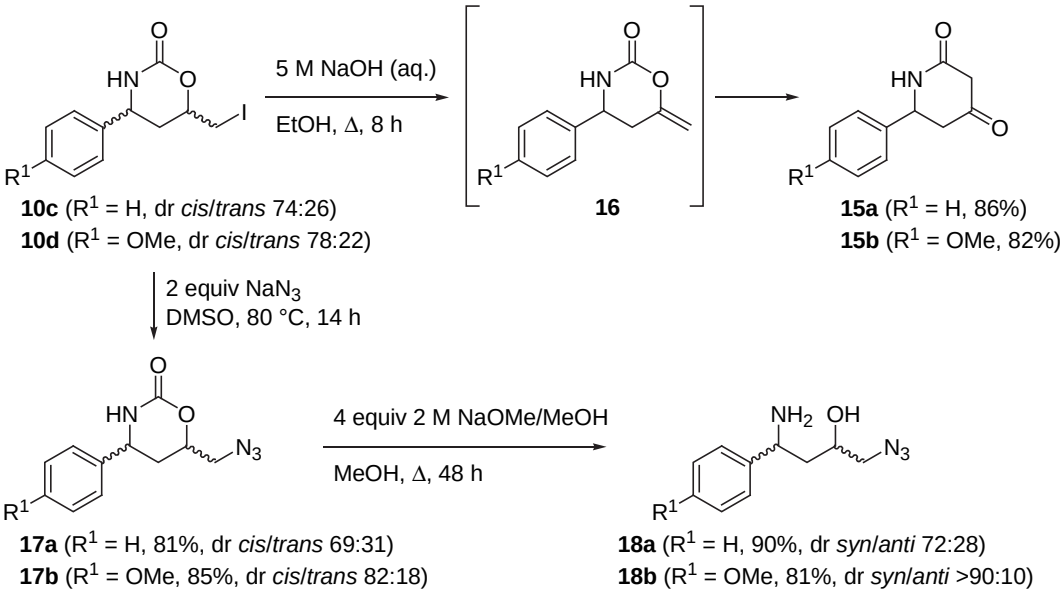


Figure 3. Possible transition states in the formation of the *cis*- and *trans*-diastereomers **10** and **12**.

and represent key intermediates for further synthetic transformations to 6-aryl-4-hydroxypiperidin-2-ones,[27] 4-hydroxypipecolic acids,[28] (R)-(+)-2-phenylpiperidine[29] and biomimetic NADH models.[30] 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.[27] 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.[29,31] 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.[32] An early efficient preparation of 1-*tert*-butyl-6-phenylpiperidine-2,4-dione involved the addition of *N*-benzylidene-*tert*-butylamine to diketene.[33] 1-Methyl-6-phenylpiperidine-2,4-dione was synthesized in moderate yield through 1,3-dipolar cycloaddition of the appropriate nitrone with methyl 2-chlorobut-3-enoate and subsequent hydrogenolysis of the intermediate isoxazolidine.[34] 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.[35] The formation of piperidine-2,4-diones **15** from 6-(iodomethyl)-1,3-oxazinan-2-ones **10** is believed to proceed via initial base-induced elimination of hydrogen iodide to give 6-methylene-1,3-oxazinan-2-ones **16** followed by basic hydrolysis of the oxazinanone and intramolecular C-carbamoylation of the formed enolate. The alkoxide-catalyzed rearrangement of isomeric

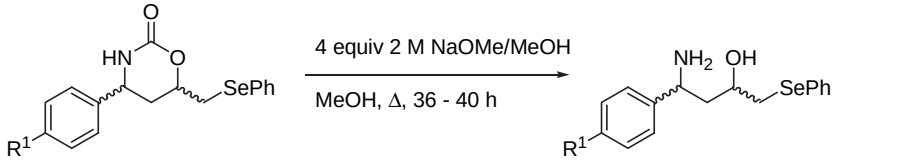


Scheme 5.

2-alkylidene-1,3-oxazinan-6-ones to piperidine-2,4-diones has been described more than 40 years ago.[36] 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 **10c**,**d** could be successfully substituted upon heating with sodium azide in DMSO, which efficiently afforded the corresponding 6-(azidomethyl)-1,3-oxazinan-2-ones **17** (Scheme 5). The absence of a tethered leaving group in the C-6 substituent of 6-(azidomethyl)-1,3-oxazinan-2-ones **17**, inhibiting base-induced elimination to 6-methylene-1,3-oxazinan-2-ones **16**, allowed the solvolysis to 4-amino-4-aryl-1-azidobutan-2-ols **18** (81–90% yield) upon heating with sodium methoxide in methanol. Upon considering the aryl group as a carboxyl synthon,[37] the azido amino-alcohols **18** 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,[38] which are also constituents of the antibiotic cyclopeptide natural products biphenomycins,[39] K-582 type antibiotics[40] and β-lactam antibiotic clavalanine.[41]

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.[42]



10e (R^1 = H, dr *cis*/*trans* 46:54)
10f (R^1 = MeO, dr *cis*/*trans* 44:56)

19a (R^1 = H, 84%, dr *syn*/*anti* 2:3)
19b (R^1 = MeO, 80%, dr *syn*/*anti* 49:51)

Scheme 6.

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 75 MHz 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 min 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 h. The reaction was quenched with 2 N aq Na_2SO_3 (for reaction with Br_2) or 2 N aq $Na_2S_2O_3$ (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, $CDCl_3$): δ=1.86 (dt, 1H, J=13.76 Hz, 11.56 Hz, 5-CH(*H*)), 2.47 (dddd, 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_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=32.6, 35.3, 55.2, 75.8, 126.2, 129.0, 129.3, 140.2, 153.1. IR (ATR, cm^{-1}): ν=3225 (NH), 3121, 1696 (*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, $CDCl_3$): δ=2.17 (dddd, 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 (dddd, 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_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=32.3, 32.8, 52.3, 72.4, 125.9, 128.4, 129.2, 141.2, 153.2. IR (ATR, cm^{-1}): ν=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). Colourless crystals; mp: 138.2–140.2 °C; yield 36%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.83 (dt, 1H, J=13.76 Hz, 11.56 Hz, 5-CH(*H*)), 2.41 (dddd, 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_3O), 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, $CDCl_3$): δ=32.6, 35.4, 54.7, 55.5, 75.8, 114.6, 127.5, 132.1, 153.0, 160.0. IR (ATR, cm^{-1}): ν=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, $CDCl_3$): δ=2.13 (dddd, 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_3O), 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, $CDCl_3$): δ=32.2, 32.9, 51.8, 55.5, 72.5, 114.5, 127.0, 133.1, 153.1, 159.6. IR (ATR, cm^{-1}): ν=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). Colourless crystals; mp: 181.5–183.5 °C; yield 31%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=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 (dddd, 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_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=5.5, 36.9, 55.2, 76.1, 126.2, 129.0, 129.3, 140.2, 153.1. IR (ATR, cm^{-1}): ν=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, $CDCl_3$): δ=2.20 (dddd, 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 (dddd, 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_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=5.3, 34.4, 52.3, 72.7, 125.8, 128.4, 129.2, 141.2, 153.2. IR (ATR, cm^{-1}): ν=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, $CDCl_3$): δ=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_3O), 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, $CDCl_3$): δ=5.7, 37.0, 54.6, 55.5, 76.0, 114.6, 127.5, 132.1, 153.3, 160.0. IR (ATR, cm^{-1}): ν=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, $CDCl_3$): δ=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_3O), 4.25 (dddd, 1H, *J*=9.1 Hz, 7.15 Hz, 4.95 Hz, 3.03 Hz, CHO), 4.69–4.73 (m, 1H, CHN), 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, $CDCl_3$): δ=5.3, 34.5, 51.7, 55.5, 72.8, 114.5, 127.0, 133.1, 153.3, 159.6. IR (ATR, cm^{-1}): ν=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, $CDCl_3$): δ=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, $CDCl_3$): δ=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 $C_{17}H_{17}NO_2Se$: 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%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.74 (dt, 1H, *J*=13.76 Hz, 11.56 Hz, 5-CH(*H*)$_{cis}$), 2.18–2.24 (m, 2H, 5-CH(*H*)$_{trans}$), 2.47 (ddt, 1H, *J*=13.76 Hz, 4.40 Hz, 1.9 Hz, 5-CH(*H*)$_{cis}$), 2.97 (dd, 1H, *J*=12.80 Hz, 9.2 Hz, CH(*H*)Se$_{trans}$), 2.98 (dd, 1H, *J*=13.07 Hz, 8.4 Hz, CH(*H*)Se$_{cis}$), 3.26 (dd, 1H, *J*=12.80 Hz, 4.5 Hz, CH(*H*)Se$_{trans}$), 3.33 (dd, 1H, *J*=12.93 Hz, 4.68 Hz, CH(*H*)Se$_{cis}$), 3.81 (s, 3H, CH_3O_{cis}), 3.82 (s, 3H, CH_3O_{trans}), 4.27–4.35 (m, 1H, CHO$_{trans}$), 4.44–4.53 (m, 1H, CHO$_{cis}$), 4.51 (dd, 1H, *J*=11.28 Hz, 4.3 Hz, CHN$_{cis}$), 4.57–4.62 (m, 1H, CHN$_{trans}$), 5.15 (br s, 1H, NH$_{cis}$), 5.38 (br s, 1H, NH$_{trans}$), 6.86–7.54 (m, 18H, Ar–H$_{cis+trans}$). ^{13}C NMR (75 MHz, $CDCl_3$): 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), 3102, 1685 (*C*=O). MS (ES, M+H$^+$, pos): *m*/*z* 378/376 (M+H$^+$, 100). Anal. Calcd for $C_{18}H_{19}NO_3Se$: 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) were 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 h. 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 Et_2O (2×100 mL). The combined organic layers were dried ($MgSO_4$), 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 NH_4Cl solution and extracted with Et_2O (2×30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/Et_2O 6/1) to give compounds **11**.

*4.2.15. Benzyl N-benzyl-N-(1-phenyl-3-butenyl)carbamate (**11a**).* Colourless oil; yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$, recorded at 50 °C): δ=2.67 (t, 2H, *J*=7.2 Hz, CH_2CH=), 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, =CH_2), 5.17 (s, 2H, OCH_2), 5.32–5.43 (m, 1H, CHN), 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%. ^{1}H NMR (300 MHz, $CDCl_3$, recorded at 50 °C): δ=2.63 (t, 2H, *J*=7.2 Hz, CH_2CH=), 3.78 (s, 3H, CH_3O), 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, =CH_2), 5.17 (s, 2H, OCH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 min 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 h. 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, $CDCl_3$): δ=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, 2×C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=33.0, 34.2, 50.6, 55.8, 71.6, 126.3, 128.0, 128.3, 128.4, 128.9, 129.4, 136.5, 139.5, 153.6. IR (ATR, cm^{-1}): ν=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, $CDCl_3$): δ=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_3O), 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, $CDCl_3$): δ=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}): ν=1689 (*C*=O). MS (ES, pos): *m*/*z* 390/392 (M+H$^+$, 100). Purity >90% as determined by reverse phase HPLC analysis (integration at 220 nm).

*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, $CDCl_3$): δ=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, 2×C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=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, 153.7. IR (ATR, cm^{-1}): ν=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. trans-3-Benzyl-6-(iodomethyl)-4-(4-methoxyphenyl)-1,3-oxazinan-2-one (**12d**).* Isolated together with the *cis*-isomer **12d** as 91/9 mixture by column chromatography (EtOAc). Viscous yellow oil; yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=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_3O), 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ=6.2, 36.0, 50.4, 55.3, 55.5, 71.9, 114.7, 127.4, 127.9, 128.3, 128.9, 131.4, 136.6, 139.6, 153.6, 159.6. IR (ATR, cm^{-1}): ν=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 *trans*/*cis* mixture by column chromatography (EtOAc). Viscous colourless oil; yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.93 (dt, 1H, *J*=14.03 Hz, 11.4 Hz, 5-CH(H)$_{cis}$), 2.06 (ddd, 1H, *J*=13.76 Hz, 10.7 Hz, 5.8 Hz, 5-CH(*H*)$_{trans}$), 2.27 (dt, 1H, *J*=13.76 Hz, 2.48 Hz, 5-CH(*H*)$_{trans}$), 2.52 (ddd, 1H, *J*=13.97 Hz, 5.9 Hz, 1.9 Hz, 5-CH(*H*)$_{cis}$), 2.85 (dd, 1H, *J*=12.66 Hz, 8.81 Hz, CH(H)Se$_{trans}$), 2.94 (dd, 1H, *J*=12.93 Hz, 8.26 Hz, CH(*H*)Se$_{cis}$), 3.20 (dd, 1H, *J*=12.93 Hz, 4.40 Hz, CH(*H*)Se$_{trans}$), 3.30 (dd, 1H, *J*=12.93 Hz, 4.68 Hz, CH(*H*)Se$_{cis}$), 3.54 (d, 1H, *J*=15.13 Hz, NCH(*H*)$_{cis}$), 3.60 (d, 1H, *J*=15.13 Hz, NCH(*H*)$_{trans}$), 4.22–4.38 (m, 3H, CHO$_{trans+cis}$ and CHN$_{cis}$), 4.43 (dd, 1H, *J*=5.78 Hz, 2.20 Hz, CHN$_{trans}$), 5.22 (d, 1H, *J*=14.86 Hz, NCH(*H*)$_{cis}$), 5.36 (d, 1H, *J*=15.13 Hz, NCH(*H*)$_{trans}$), 7.03–7.51 (m, 30H, Ar–H$_{cis+trans}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=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}): ν=1688 (*C*=O). MS (ES, pos): *m*/*z* 436/438 (M+H$^+$, 100). Anal. Calcd for $C_{24}H_{23}NO_2Se$: 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 *trans*/*cis* mixture by column chromatography (EtOAc). Viscous yellow oil; yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.92 (dt, 1H, *J*=14.31 Hz, 11.5 Hz, 5-CH(*H*)$_{cis}$), 2.02 (ddd, 1H, *J*=13.62 Hz, 10.87 Hz, 5.6 Hz, 5-CH(*H*)$_{trans}$), 2.22 (dt,

1H, J=13.48 Hz, 2.48 Hz, 5-CH(H)$_{trans}$), 2.49 (ddd, 1H, J=13.97 Hz, 6.1 Hz, 1.6 Hz, 5-CH(H)$_{cis}$), 2.85 (dd, 1H, J=12.80 Hz, 8.9 Hz, CH(H)Se$_{trans}$), 2.95 (dd, 1H, J=12.93 Hz, 8.53 Hz, CH(H)Se$_{cis}$), 3.21 (dd, 1H, J=12.80 Hz, 4.5 Hz, CH(H)Se$_{trans}$), 3.30 (dd, 1H, J=12.93 Hz, 4.68 Hz, CH(H)Se$_{cis}$), 3.55 (d, 1H, J=15.13 Hz, NCH(H)$_{cis}$), 3.60 (d, 1H, J=15.13 Hz, NCH(H)$_{trans}$), 3.83 (s, 3H, CH$_3$O$_{cis}$), 3.85 (s, 3H, CH$_3$O$_{trans}$), 4.21–4.34 (m, 3H, CHO$_{trans+cis}$ and CHN$_{cis}$), 4.37 (dd, 1H, J=5.50 Hz, 2.75 Hz, CHN$_{trans}$), 5.19 (d, 1H, J=15.13 Hz, NCH(H)$_{cis}$), 5.34 (d, 1H, J=15.13 Hz, NCH(H)$_{trans}$), 6.88–7.51 (m, 28H, Ar–H$_{cis+trans}$). ^{13}C NMR (75 MHz, CDCl$_3$): δ=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, 127.80, 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}): ν=1687 (C=O). MS (ES, pos): m/z 466/468 (M+H$^+$, 100). Anal. Calcd for $C_{25}H_{25}NO_3Se$: 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_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was crystallized from CH_2Cl_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,[27] 166–168 °C for (R)-(+)-**15a**,[29] 164–168 °C[32]); yield 86%. ^{1}H NMR (300 MHz, CDCl$_3$): δ=2.77 (dd, 1H, J=16.0 Hz, 9.5 Hz, 5-CH(H)), 2.90 (dd, 1H, J=16.0 Hz, 4.40 Hz, 5-CH(H)), 3.39 (s, 2H, 3-CH$_2$), 4.82 (ddd, 1H, J=9.56 Hz, 4.5 Hz, 1.7 Hz, CH), 6.25 (br s, 1H, NH), 7.31–7.47 (m, 5H, C$_6$H$_5$). ^{13}C NMR (75 MHz, CDCl$_3$): δ=47.1, 47.3, 52.9, 126.1, 128.9, 129.5, 139.3, 169.3, 202.4. IR (ATR, cm^{-1}): ν=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.[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,[27] 171–172 °C[43]); yield 82%. ^{1}H NMR (300 MHz, CDCl$_3$): δ=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-CH$_2$), 3.82 (s, 3H, OCH$_3$), 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). ^{13}C NMR (75 MHz, CDCl$_3$): 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 H_2O (30 mL) and extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine. The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. Crystallisation of the residue from CH_2Cl_2/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%. ^{1}H NMR (300 MHz, CDCl$_3$): 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)$_{cis}$), 2.36 (ddd, 1H, J=13.8 Hz, 10.5 Hz, 5.8 Hz, 5-CH(H)$_{trans}$), 3.43 (dd, 1H, J=13.07 Hz, 5.1 Hz, CH(H)N$_{3,trans}$), 3.49–3.56 (m, 3H, CH(H)N$_{3,trans}$ and CH(H)N$_{3,cis}$), 4.31–4.38 (m, 1H, CHO$_{trans}$), 4.55 (dddd, 1H, J=11.70 Hz, 5.0 Hz, 5.0 Hz, 2.1 Hz, CHO$_{cis}$), 4.62 (dd, 1H, J=11.56 Hz, 4.40 Hz, CHN$_{cis}$), 4.82 (dt, 1H, J=5.8 Hz, 3.0 Hz, CHN$_{trans}$), 5.26 (br s, 1H, NH$_{cis}$), 5.58 (br s, 1H, NH$_{trans}$), 7.29–7.44 (m, 10H, 2×C$_6$H$_5$). ^{13}C NMR (75 MHz, CDCl$_3$): 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%. ^{1}H NMR (300 MHz, CDCl$_3$): 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 (ddd, 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)N$_{3,trans}$), 3.47–3.53 (m, 1H, CH(H)N$_{3,trans}$), 3.53 (dd, 1H, J=13.21 Hz, 4.95 Hz, CH(H)N$_{3,cis}$), 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 (dddd, 1H, J=10.25 Hz, 5.0 Hz, 5.0 Hz, 2.7 Hz, CHO$_{trans}$), 4.48–4.56 (m, 1H, CHO$_{cis}$), 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, CDCl$_3$): δ=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}): ν=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_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2×50 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$_3$): δ=1.73–1.84 (m, 3H, 3-CH(H)$_{syn}$ and 3-CH(H)$_{anti}$), 1.93 (ddd, 1H, J=14.31 Hz, 8.67 Hz, 3.7 Hz, 3-CH(H)$_{anti}$), 3.22–3.34 (m, 4H, CH(H)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, CHN$_{anti}$), 7.23–7.40 (m, 10H, Ar–H$_{anti+syn}$). ^{13}C NMR (75 MHz, CDCl$_3$): δ=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}): ν=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$_3$): δ=1.72–1.85 (m, 2H, 3-CH(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), 3.98–4.03 (m, 1H, CHN), 4.07–4.15 (m, 1H, CHO), 6.87–6.90 (m, 2H, Ar–H), 7.15–7.19 (m, 2H, Ar–H). ^{13}C NMR (75 MHz, CDCl$_3$): δ=40.5, 55.3, 56.1, 56.8, 71.9, 114.2, 126.4, 138.6, 158.8. IR (ATR, cm^{-1}): ν=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_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2×50 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, $CDCl_3$): δ=1.75 (dt, 1H, J=14.03 Hz, 10.46 Hz, 3-CH(H)$_{anti}$), 1.90–2.02 (m, 3H, 3-CH(H)$_{syn}$ and 3-CH(H)$_{anti}$), 2.82–3.33 (m, 8H, CH(H)Se$_{anti+syn}$ and NH$_{2,anti+syn}$), 3.87–3.95 (m, 1H, CHO$_{syn}$), 4.01 (dd, 1H, J=10.73 Hz, 2.75 Hz, CHN$_{anti}$), 4.04–4.12 (m, 1H, CHO$_{anti}$), 4.33 (t, 1H, J=5.6 Hz, CHN$_{syn}$), 7.19–7.53 (m, 20H, Ar–H$_{anti+syn}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=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}): ν=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, $CDCl_3$): δ=1.73 (dt, 1H, J=14.03 Hz, 10.46 Hz, 3-CH(H)$_{anti}$), 1.88–1.99 (m, 3H, 3-CH(H)$_{syn}$ and 3-CH(H)$_{anti}$), 2.95–3.11 (m, 4H, CH(H)Se$_{anti+syn}$), 3.80 (s, 3H, CH_3O_{syn}), 3.81 (s, 3H, CH_3O_{anti}), 3.86–3.947 (m, 1H, CHO$_{syn}$), 3.97 (dd, 1H, J=10.73 Hz, 3.03 Hz, CHN$_{anti}$), 4.03–4.11 (m, 1H, CHO$_{anti}$), 4.30 (t, 1H, J=5.6 Hz, CHN$_{syn}$), 6.85–7.53 (m, 18H, Ar–H$_{anti+syn}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=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}): ν=3338 (OH), 3259 (NH). MS (ES, M+H$^+$, pos): m/z 333/335 (100). Anal. Calcd for $C_{17}H_{21}NO_2Se$: 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 (colourless blocks) by slow evaporation from a diethyl ether solution at room temperature. $C_{12}H_{14}BrNO_3$, M_r=300.15, monoclinic, space group $P2_1/c$, a=14.6488(9) Å, b=6.2920(4) Å, c=15.2272(7) Å, U=1275.36(13) Å^3, Z=4, T=173(2) K, 9756 reflections measured, 2290 unique (R_{int}=0.057). The final $wR(F^2)$ 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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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.113. These data include MOL files and InChiKeys of the most important compounds described in this article.

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