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Efficient Synthesis of 5-Chalcogenyl-1,3-oxazin-2-ones by Chalcogen-Mediated Yne–Carbamate Cyclisation: An Experimental and Theoretical Study

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A very efficient synthesis of 5-chalcogenyl-1,3-oxazin-2-ones has been accomplished by the chalcogen-mediated yne–carbamate cyclisation of chiral, non-racemic *N*-Cbz-protected propargylic amines using PhXY (X = Se, S, Te; Y = Br or Cl) as electrophile sources. The reactions gave good-to-excellent yields for a wide range of substrates. In all cases the reaction was totally regioselective, occurring by a 6-*endo-dig* process regardless of the nature of the reagent and of the substituents in the starting material. This methodology permits the formation of the 1,3-oxazin-2-one moiety as well as the simultaneous installation of a chalcogen functionality onto the heterocyclic ring. The experimental results have been rationalised by theoretical studies at the B3LYP/6-311G* level of theory.

Introduction

Carbamates are an important class of compounds that show interesting properties and find wide utility in several areas, such as pharmaceuticals,[1] agrochemicals[2] and materials.[3] Although there are a variety of methods for the synthesis of this kind of compound,[4] the development of practical and efficient methods for the preparation of cyclic carbamates, especially those that are densely functionalised, is of great interest.

On the other hand, the interest in organochalcogenide compounds has increased considerably in the last decade, because the introduction of chalcogen groups into organic molecules modifies their physical and chemical properties as well as biological activities. The polarisation of the carbon–chalcogen bond leads to a wide range of applications in organic synthesis,[5] because it allows the introduction of new functionalities through the replacement of the carbon–chalcogen bond by carbon–halogen, carbon–lithium or carbon–carbon bonds. Organochalcogenides show potential biological activities such as antiviral, antihypertensive, antioxidant, antimicrobial and anticancer properties.[6] Consequently, a number of methods have been reported in recent years that lead to the synthesis of this kind of compound.[7] However, the development of new and efficient protocols for the synthesis of functionalised chalcogen-substituted heterocycles remains an important challenge in organic chemistry.[8] Indeed, several important heterocycles, such as indoles,[9] pyrroles,[10] benzofurans,[11] benzothiophenes,[12] benzoselenophenes,[11b,13] thiophenes,[14] furans[15] and benzopyrans,[16] have been synthesised by electrophilic cyclisation of suitable unsaturated systems with a wide range of internal nucleophilic groups. These strategies are of particular interest because valuable hetero- and carbocycles can be readily formed under relatively mild conditions.

Bearing in mind these bibliographic records and our own experience,[17] we reasoned that the electrophilic cyclisation reactions of *N*-Cbz-protected propargylic amines by using selenium, sulfur or tellurium electrophilic reagents could provide an interesting synthesis of functionalised chalcogen-substituted heterocycles, and a study of the regioselectivity of the cyclisation reaction would be of significant interest. When an *N*-Cbz-protected propargylic amine of type **1** is subjected to an electrophilic *O*-cyclisation process, two reaction modes are possible: the 6-*endo-dig* mode that should yield 1,3-oxazin-2-ones **2** and the 5-*exo-dig* mode that should yield 1,3-oxazolidin-2-ones **5** (Scheme 1). Several authors have proved that both cyclisation modes are possible in reactions carried out on related substrates, and have shown that the regioselectivity of the reaction depends on the structure of the starting material and the nature of the reagent or catalyst.[18–22]

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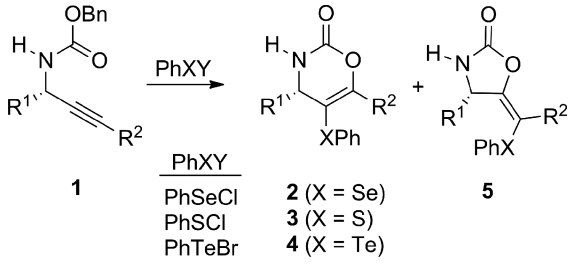

Scheme 1. Electrophilic yne–carbamate chalcogen-cyclisation of *N*-Cbz-protected propargylic amines.

In our previous paper[17] on the *O*-cyclisation reactions of *N*-Cbz-protected propargylic amines promoted by halogens, a totally regioselective 6-*endo-dig* process was observed. However, in the metal-catalysed cyclisation of *N*-Boc-protected propargylic amines described by Carretero and co-workers,[20] the reaction took place by the intramolecular 5-*exo-dig* mode to afford five-membered-ring products **5**. Also, metal-catalysed 5-*exo-dig* cyclisation of carbamate-protected propargylic alcohols[21] and ureas[22] providing five-membered carbamates and carbamimidates, respectively, have recently been described. Therefore good control of the regioselectivity of the *O*-chalcogen cyclisation reaction is essential for the selective preparation of **2** or **5** (Scheme 1). In this paper we report our experimental results on such a reaction. To the best of our knowledge, there is no protocol describing the simultaneous formation of the 1,3-oxazin-2-one system and the installation of a chalcogen functionality onto the heterocycle ring by using *N*-Cbz-protected propargylic amines as substrates through yne–carbamate electrophilic cyclisation reactions. Also, the mechanism of this reaction has been investigated theoretically.

Results and Discussion

The required starting materials, *N*-Cbz-protected propargylic amines **1**, were readily prepared by the addition of terminal alkynes to imines generated in situ from α-amido sulfones in the presence of diethylzinc and BINOL-type ligands as catalyst following our previously reported method.[23] To establish the appropriate reaction conditions for the electrophilic cyclisation we treated *N*-Cbz-1,3-diphenylprop-2-yn-1-amine (**1a**) with phenylselenyl chloride (1.5 equiv.) in acetonitrile (2.0 mL) at 0 °C. Under these reaction conditions we obtained the corresponding 5-phenylselenylated-1,3-oxazin-2-one **2a** with an endocyclic double bond as the only product with total regioselectivity and in quantitative yield (99%). These reaction conditions allowed us to synthesise a wide range of 4,6-disubstituted 3,4-dihydro-5-phenylselenylated-1,3-oxazin-2-ones **2** through a 6-*endo-dig* *O*-cyclisation process in good-to-excellent yields. Several *N*-Cbz-protected propargylic amines **1** derived from the addition of phenylacetylene to *N*-Cbz-imines of substituted benzaldehydes (Table 1, entries 1–3) were transformed into the corresponding 5-phenylselenylated 1,3-oxazin-2-ones **2** in good-to-excellent yields. Both electron-withdrawing (Cl) and -donating (Me) substituents were well tolerated at *para* and *ortho* positions, with yields ranging from 88 to 99%. In addition, the phenylseleno cyclisation of *N*-Cbz-protected propargylic amines **1** derived from alkyl-substituted imines also gave the corresponding products in very good yield (90%, Table 1, entry 4). Various *N*-Cbz-protected propargylic amines **1** bearing different aromatic and aliphatic groups attached to the alkyne moiety afforded the corresponding products **2** in excellent yields in the most cases (Table 1, entries 5–7); although the aryl-substituted starting materials **1e**,**f** afforded the corresponding phenylselenylated cyclisation products in excellent yields (96–99%), the 2-phenylethyl-substituted **1g** only gave a moderate yield (71%).

Table 1. Electrophilic yne–carbamate cyclisation of *N*-Cbz-protected propargylic amines **1** to 5-chalcogenyl-1,3-oxazin-2-ones **2**.[a]

Entry	1	R^1	R^2	PhXY	Time [h]	Product	Yield [%][b]
1	**1a**	Ph	Ph	PhSeCl	0.25	**2a**	99
2	**1b**	4-ClC_6H_4	Ph	PhSeCl	0.25	**2b**	88
3	**1c**	2-MeC_6H_4	Ph	PhSeCl	0.25	**2c**	99
4	**1d**	*n*-Butyl	Ph	PhSeCl	0.5	**2d**	90
5	**1e**	Ph	4-FC_6H_4	PhSeCl	0.25	**2e**	99
6	**1f**	Ph	2-$MeOC_6H_4$	PhSeCl	0.25	**2f**	96
7	**1g**	Ph	$PhCH_2CH_2$	PhSeCl	0.5	**2g**	71
8	**1a**	Ph	Ph	PhSCl	0.5	**3a**	92
9	**1b**	4-ClC_6H_4	Ph	PhSCl	1	**3b**	93
10	**1c**	2-MeC_6H_4	Ph	PhSCl	0.5	**3c**	78
11	**1h**	$C_6H_5CH_2CH_2$	Ph	PhSCl	0.5	**3h**	90
12	**1e**	Ph	4-FC_6H_4	PhSCl	1	**3e**	99
13	**1f**	Ph	2-$MeOC_6H_4$	PhSCl	0.25	**3f**	79
14	**1a**	Ph	Ph	PhTeBr	4	**4a**	75
15	**1i**	4-MeC_6H_4	Ph	PhTeBr	3	**4i**	87
16	**1j**	Cyclohexyl	Ph	PhTeBr	20	**4j**	58
17	**1k**	Ph	4-ClC_6H_4	PhTeBr	4	**4k**	65
18	**1l**	Ph	2-Thienyl	PhTeBr	2	**4l**	75
19	**1g**	Ph	$PhCH_2CH_2$	PhTeBr	4	**4g**	80

[a] Reagents and conditions: **1** (0.1 mmol), phenylselenyl chloride (0.15 mmol), acetonitrile (2.5 mL, entries 1–7); **1** (0.1 mmol), phenylsulfenyl chloride in 1,2-dichloroethane (0.4 M, 0.15 mmol), acetonitrile (2.5 mL, entries 8–13); **1** (0.1 mmol), phenyltellanyl bromide in 1,2-dichloroethane (0.5 M, 0.15 mmol), acetonitrile (2.5 mL, entries 14–19). [b] Yield of isolated product.

Under similar reaction conditions, we next evaluated the phenylsulfenyl cyclisation reaction of several *N*-Cbz-protected propargylic amines **1**. Thus, the starting material dissolved in acetonitrile was treated with 1.5 equiv. of a freshly prepared 0.4 M solution of phenylsulfenyl chloride in 1,2-dichloroethane at 0 °C.[24] The reaction proceeded to give good-to-excellent yields of 5-phenylthio-1,3-oxazin-2-ones **3** (Table 1, entries 8–13). Aromatic groups with an electron-withdrawing substituent at the *para* position provided the cyclisation products in excellent yields (93–99%; Table 1, entries 9 and 12), whereas the utilisation of propargylic amines with aromatic groups bearing an electron-donating group at the *ortho* position gave the desired products in somewhat lower yields (78–79%; Table 1, entries 10 and 13). The cyclisation reaction of a propargylic amine derived from an aliphatic aldehyde occurred in high yield (90%; Table 1, entry 11).

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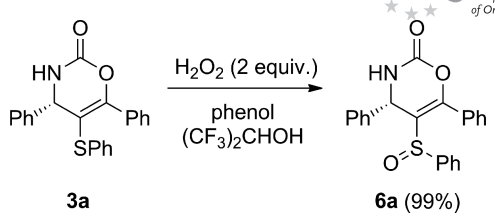
Finally, *N*-Cbz-protected propargylic amines **1** dissolved in acetonitrile were treated with a freshly prepared 0.5 M solution of phenyltelluryl bromide in 1,2-dichloroethane.[25] These yne–carbamate cyclisation reactions required longer times and provided the 5-phenyltellanyl-1,3-oxazin-2-ones **4** in moderate-to-high yields (58–87%; Table 1, entries 14–19). The cyclisation of propargylic amines derived from benzaldehyde and *p*-tolylaldehyde yielded the corresponding products in good yields (75–87%; Table 1, entries 14 and 15). However, the utilisation of the propargylic amine derived from cyclohexanecarbaldehyde **1j** provided the desired 1,3-oxazin-2-one **4j** in moderate yield (58%; Table 1, entry 16). Both aromatic and heteroaromatic groups attached to the alkyne moiety were tolerated by this procedure (Table 1, entries 17 and 18). In addition, 2-phenylethyl-substituted **1g** gave the corresponding 1,3-oxazin-2-one **4g** in 80% yield (Table 1, entry 19).

The structures of 5-phenylchalcogenyl-1,3-oxazin-2-ones **2**–**4** were elucidated by X-ray diffraction analysis and spectroscopic methods. Due to the failure to obtain appropriate monocrystals of products **2**–**4**, 5-phenylthio-1,3-oxazin-2-one **3a** was subjected to oxidative conditions,[9a] yielding a diastereomeric mixture of the corresponding sulfoxide derivative **6a**, from which the major diastereomer was isolated (Scheme 2). An X-ray diffraction analysis of this diastereomer allowed us to establish its structure and unequivocally confirmed the existence of the six-membered ring, as illustrated in Figure 1.[26]

A ^{13}C NMR spectroscopic analysis was carried out to ensure that all the chalcogen-mediated cyclisation reactions proceeded by a 6-*endo*-*dig* mechanism. We compared the ^{13}C NMR signals of the four carbon atoms in the six-membered ring containing the cyclic carbamate (Table 2). In the case of the 5-phenylthio-1,3-oxazin-2-ones **3**, the carbonyl group gives a signal at δ = 152–153 ppm (when R^2 is aromatic), the quaternary olefinic =C–O resonates at δ = 149–150 ppm, the quaternary olefinic S–C= appears at high field at δ = 106–107 ppm and the CH appears at δ = 54–60 ppm. In the case of 5-phenylselenyl-1,3-oxazin-2-ones **2**, the carbonyl group gives a signal at δ = 150–151 ppm (when R^2 is aromatic) and δ = 154 ppm (when R^2 is aliphatic), the quaternary olefinic =C–O resonates at δ = 149–152 ppm, the quaternary olefinic Se–C= appears at high field at δ = 103–105 ppm and the CH appears at δ = 55–60 ppm. Finally, the ^{13}C NMR spectra of 5-phenyltellanyl-1,3-oxazin-2-ones **4** shows the signal of the carbonyl group at δ = 150–151 ppm (when R^1 and R^2 are aromatic) and δ = 152–154 ppm (when R^1 or R^2 is aliphatic), the quaternary olefinic =C–O resonates at δ = 150–152 ppm, the quaternary



Scheme 2. Oxidation of **3a** to yield **6a**.

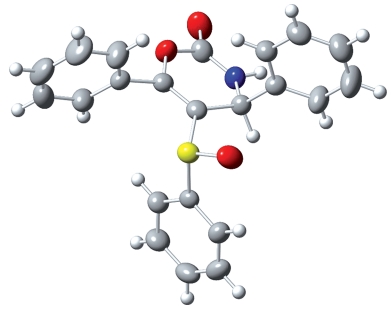


Figure 1. ORTEP plot of the X-ray structure of compound **6a**. The thermal ellipsoids are drawn at the 50% probability level.

Table 2. ^{13}C NMR signals of the four carbon atoms in the six-membered ring containing the cyclic carbamate in compounds **2**–**4**.

Entry	**2**–**4**	X	R^1	R^2	δ [ppm]			
					C=O[a]	=C–O[a]	X–C=	CH
1	**3a**	S	Ph	Ph	152.93	150.06	106.79	58.78
2	**3b**	S	4-ClC_6H_4	Ph	153.03	149.94	106.48	58.13
3	**3c**	S	2-MeC_6H_4	Ph	153.31	149.89	106.32	55.22
4	**3h**	S	$PhCH_2CH_2$	Ph	153.42	151.01	106.68	53.93
5	**3e**	S	Ph	4-FC_6H_4	151.99	149.80	106.83	58.88
6	**3f**	S	Ph	2-$MeOC_6H_4$	157.44	150.14	105.93	60.17
7	**2a**	Se	Ph	Ph	151.50	150.27	103.85	60.21
8	**2b**	Se	4-ClC_6H_4	Ph	151.61	150.12	103.49	59.62
9	**2c**	Se	2-MeC_6H_4	Ph	151.84	150.03	103.38	56.75
10	**2d**	Se	*n*-butyl	Ph	151.74	151.65	104.23	55.75
11	**2e**	Se	Ph	4-FC_6H_4	150.61	150.11	104.01	60.35
12	**2f**	Se	Ph	2-$MeOC_6H_4$	157.44	150.14	105.93	60.17
13	**2g**	Se	Ph	$PhCH_2CH_2$	153.95	149.88	103.11	60.16
14	**4a**	Te	Ph	Ph	151.86	150.38	89.14	62.54
15	**4i**	Te	4-MeC_6H_4	Ph	151.85	150.33	89.49	62.37
16	**4j**	Te	cyclohexyl	Ph	152.19	152.19	88.53	62.50
17	**4k**	Te	Ph	4-ClC_6H_4	150.91	150.09	89.82	62.85
18	**4l**	Te	Ph	2-thienyl	149.95	146.27	88.46	63.22
19	**4g**	Te	Ph	$PhCH_2CH_2$	154.56	150.08	89.41	63.21

[a] Signals could be exchanged.

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olefinic Te–C= appears at high field at δ = 88–89 ppm and the CH appears at δ = 62–63 ppm. Only in the case of substrates with an *ortho* substituent or with a heterocyclic ring are small deviations from these values observed (see Table 2, entries 6, 12, and 18).

Determination of the enantiomeric excesses by chiral HPLC analysis of the products showed no epimerisation at the stereogenic centre regardless of the nature of the reagent and of the reaction time.

The 3,4-dihydro-5-chalcogenyl-1,3-oxazin-2-ones **2**–**4** obtained by the electrophilic yne–carbamate cyclisation reactions are versatile compounds for the construction of more complex structures, especially considering the reactivity of organochalcogen derivatives towards halogens and Li/Se exchange reactions.[27]

To understand the mechanism of the chalcogen-mediated yne–carbamate cyclisation of *N*-Cbz-protected propargylic amine **1a**, and particularly its regioselectivity to yield the six-membered 5-phenylselanyl-1,3-oxazin-2-one **2a**, a theoretical study using density functional theory (DFT) at the B3LYP/6-311G* level of theory in acetonitrile was carried out (Scheme 3). It is important to note that this theoretical study was carried out by using the same starting material as in the experimental work, without any kind of approximation by using a model compound.

A study of the potential energy surface of the title reaction indicates that the cyclisation takes place through a two-step mechanism. In the first step, the selenium atom of PhSeCl electrophilically attacks the C1 or C2 carbon atom of the triple bond of the propargylic amines to provide the cationic intermediate IN1-*endo* or IN1-*exo* via the corresponding transition states TS1-*endo* or TS1-*exo*, respectively. In the second step, the benzyl group on the carbamate substituent is eliminated assisted by the halide anion Cl^- to yield the final 1,3-oxazin-2-one **2a** or 1,3-oxazolidin-2-one **5a**. The total and relative energies in acetonitrile are given in Table 3 (Figure 2).

In an earlier step of the reaction, PhSeCl forms a weak molecular complex (MC) with the π system of the triple bond of propargylic amine **1a**. The MC is located –0.8 kcal mol^{-1} below the separated reagents. The activation energies associated with the electrophilic attacks of PhSeCl on the C1 and C2 carbon atoms of propargylic amine **1a** are 4.5 (TS1-*endo*) and 11.1 kcal mol^{-1} (TS1-*exo*), respectively, and the formation of the corresponding cationic intermediates are exothermic by –12.6 (IN1-*endo*) and

Table 3. Relative energies in acetonitrile (relative to **1a** plus PhSeCl) of the stationary points involved in the cyclisation reaction of protected propargylic amine **1a** with PhSeCl.

	E [kcal mol^{-1}]
1a + PhSeCl	0.0
MC	–0.8
TS1-*endo*	4.5
TS1-*exo*	11.1
IN1-*endo*	–12.6
IN1-*exo*	–12.5
TS2-*endo*	–4.6
TS2-*exo*	–5.1
2a + $PhCH_2Cl$	–22.6
5a + $PhCH_2Cl$	–24.4

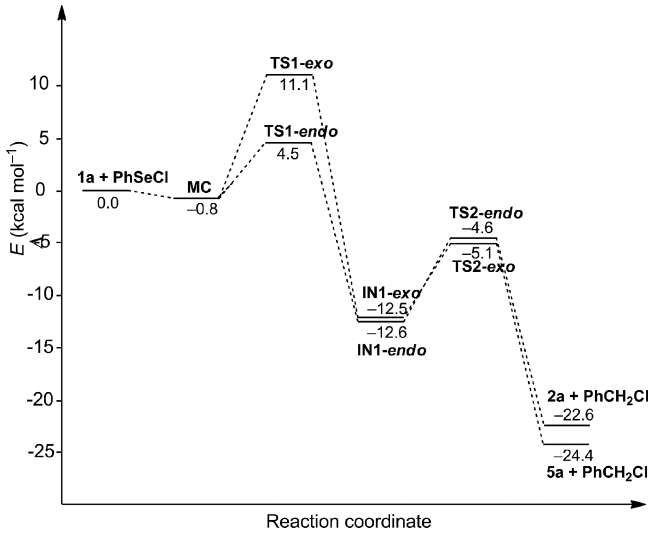
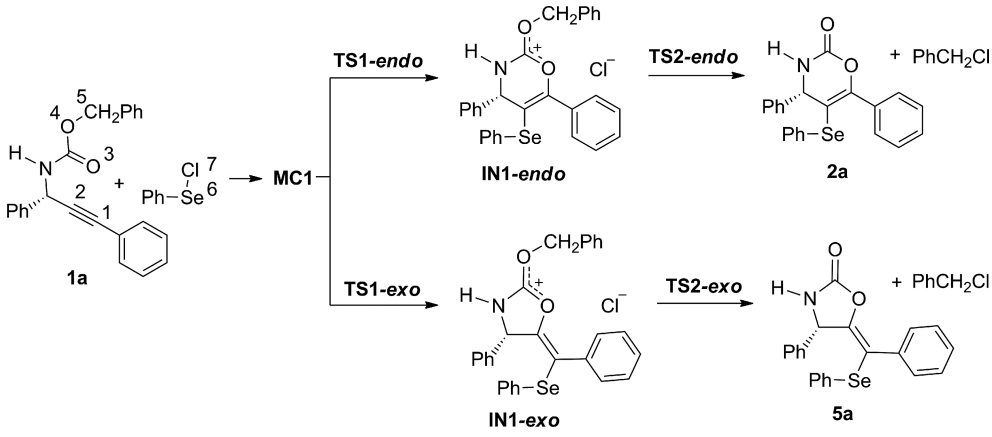


Figure 2. Relative energies in acetonitrile (in kcal mol^{-1}, relative to **1a** plus PhSeCl) of the stationary points involved in the cyclisation of **1a** with PhSeCl.



Scheme 3. Two regioisomeric reaction pathways associated with the yne–carbamate phenylselenocyclisation of propargylic amine **1a**.

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–12.5 kcal mol^{-1} (IN1-*exo*). Elimination of the benzyl group from these cationic intermediates takes place by a nucleophilic substitution of the benzyl group assisted by the chloride anion Cl^- generated in the first step of the reaction. From the corresponding intermediates, the activation energies associated with the extrusion of the benzyl group are 8.0 (TS2-*endo*) and 7.4 kcal mol^{-1} (TS2-*exo*), respectively. The formation of 1,3-oxazin-2-one **2a** and oxazolidin-2-one **5a** plus $PhCH_2Cl$ is exothermic by –22.6 and –24.4 kcal mol^{-1}, respectively.

Some important conclusions can be drawn from these data. 1) The electrophilic attack of the chalcogen PhSeCl on the triple bond of the propargylic amine **1a** is completely regioselective, TS1-*endo* being 6.6 kcal mol^{-1} lower in energy than TS1-*exo*. 2) The highly exothermic character of the first step makes this step irreversible. 3) The activation energy associated with the second step (8.0 kcal mol^{-1}) is higher than that associated with the first step (4.5 kcal mol^{-1}), thus, the elimination of the benzyl substituent is the rate-determining step (RDS) of the reaction. Consequently, although the electrophilic attack of the chalcogen PhSeCl on the propargylic amine **1a** is the regioselectivity-determining step, the benzyl elimination is the RDS of the reaction. 4) These results are similar to those of our previously reported study on halogen-mediated cyclisation of *N*-Cbz-protected propargylic amines.[17]

The geometries of the transitions states (TSs) and intermediates (INs) involved in the regioisomeric pathways associated with the chalcogen-mediated yne–carbamate cyclisation of propargylic amine **1a** are given in Figure 3. In the TSs associated with the first step of the chalcogen-mediated cyclisation reaction, the lengths of the Se6–C2(1) and O3–C1(2) forming bonds are 2.020 and 2.204 Å, respectively, in TS1-*endo*, and 2.093 and 2.154 Å, respectively, in TS1-*exo*.

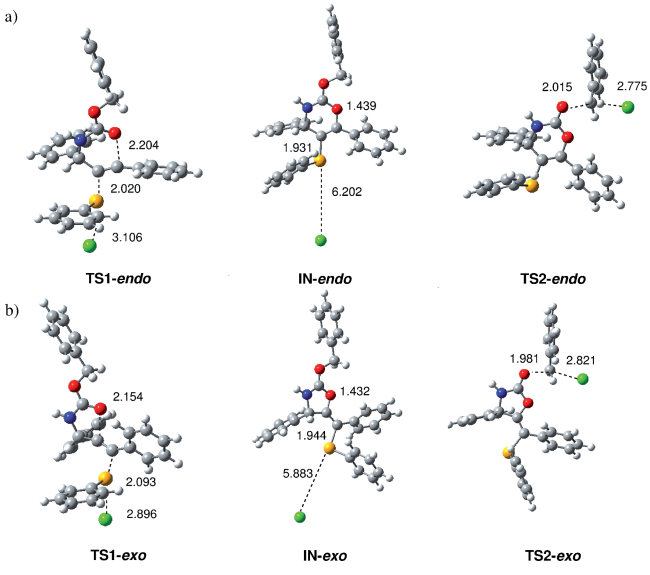

Figure 3. Geometries of the TSs and INs involved in the regioisomeric pahways associated with the chalcogen-mediated cyclisation of *N*-Cbz-protected propargylic amine **1a**. The lengths of the forming and breaking bonds are given in Ångstroms.

In the corresponding intermediates IN1-*endo* and IN1-*exo*, the lengths of the Se6–C2(1) and O3–C1(2) bonds are 1.931 and 1.439 Å, and 1.944 and 1.432 Å, respectively. These geometrical parameters indicate that the Se6–C2(1) bond formation is very advanced in the TS1s, with the O3–C2(1) bond formation more delayed.

In the TSs associated with the elimination of the benzyl group from IN1-*endo* and IN1-*exo*, the lengths of the O4–C5 breaking bond and the C5–Cl7 forming bond are 2.015 and 2.775 Å, respectively, in TS2-*endo* and 1.981 and 2.821 Å, respectively, in TS2-*exo*. Thus, in these asynchronous TSs, the O4–C5 breaking bonds are more advanced than the C5–Cl7 forming bond.

From the theoretically calculated energies and geometries of the TSs and INs involved in the two regioisomeric pathways, an explanation for the origin of the 6-*endo*-*dig* over 5-*exo*-*dig* selectivity can be given. The energy profiles given in Figure 2 show that the formation of IN1-*endo* and IN1-*exo* is irreversible. Consequently, the 6-*endo*-*dig* versus 5-*exo*-*dig* selectivity is resolved during the first step of the reaction. This first step is associated with two chemical processes: 1) the electrophilic attack of the chalcogen PhSeCl on the C1 or C2 carbon of the triple bond of the propargylic amine **1a** and 2) a ring-closing process yielding the corresponding cyclic intermediates. Analysis of the TS geometries indicates that at this stage of the reaction, the electrophilic attack of the chalcogen is very advanced. Consequently, the relative energies of TS1-*endo* and TS1-*exo* can be correlated with the local nucleophilic activation of the C1 and C2 carbon atoms of the triple bond of **1a** because the subsequent ring closure is directed by the creation of a new electrophilic centre during the electrophilic attack. Analysis of the nucleophilic P_k^- Parr functions[28] in propargylic amine **1a** indicates that the β-conjugated C2 carbon, $P_k^- = 0.30$, is the most nucleophilic centre in this molecule. Note that the nucleophilic P_k^- Parr function at the C1 carbon presents a low value of 0.01. Consequently, it is expected that the more favourable electrophilic attack of the chalcogen on the C2 carbon of **1a** generates the electrophilic centre at C1 carbon, and this behaviour forces the concomitant ring closure at this carbon via TS1-*endo*. Consequently, we can conclude that the *6-endo-dig* selectivity is determined by the electronic response of the propargylic amine **1a** to the electrophilic attack of the chalcogen more than the steric factor associated with the formation of the six-membered TS1-*endo* compared with the five membered TS1-*exo*.

Conclusions

A very efficient synthesis of 5-chalcogenyl-1,3-oxazin-2-ones has been developed by an yne–carbamate chalcogen-mediated regioselective cyclisation of chiral, non-racemic *N*-Cbz-protected propargylic amines. A broad range of substrates have been transformed under these cyclisation conditions in the presence of PhSeCl, PhSCl or PhTeBr as electrophile reagents. All the reactions proceeded through a 6-

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endo-dig mode of cyclisation to give good-to-excellent yields. This methodology permits the formation of the 1,3-oxazin-2-one moiety and the simultaneous installation of a chalcogen functionality onto the heterocyclic ring and provides a useful alternative to the reported literature protocols for preparing cyclic carbamates. In addition, DFT calculations were performed to rationalise the experimental results.

Experimental Section

General Methods: Reactions were carried out under nitrogen in round-bottomed flasks oven-dried overnight at 120 °C. Commercial reagents were used as purchased. The *N*-Cbz-protected propargylic amines **1** were prepared from the corresponding α-amido sulfones and alkynes as described in the literature.[23] Solvents were dried when necessary: dichloromethane was distilled from CaH_2. Reactions were monitored by TLC analysis by using Merck silica gel 60 F-254 thin-layer plates. Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). Melting points were determined with a Büchi M-560 apparatus. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, with a Bruker Avance 300 DPX spectrometer. ^1H and ^{13}C NMR spectra were internally referenced to the $CDCl_3$ signal (δ = 7.26 and 77.0 ppm, respectively). Chemical shifts are reported in ppm. The type of carbon was determined by DEPT experiments. HRMS were recorded with a Waters Q-TOF premier spectrometer (ESI). Specific optical rotations were measured by using sodium light (D line, λ = 589 nm). Chiral HPLC analyses were performed by using an Agilent 1100 Series chromatograph equipped with a UV diode-array detector and chiral stationary columns from Daicel.

Typical Procedure for the Phenylseleno Cyclisation of the *N*-Cbz-Protected Propargylic Amines 1: Phenylselenyl chloride (101.4 mg, 0.15 mmol) was added to a solution of *N*-Cbz-protected propargylic amine **1** (0.10 mmol) in acetonitrile (2 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was then concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **2**.

(*S*)-4,6-Diphenyl-5-(phenylselanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (2a): M.p. 157–160 °C. $[\alpha]_D^{20}$ = +157.1 (*c* = 1.00, $CHCl_3$, 86% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.59 (m, 2 H), 7.44–7.23 (m, 13 H), 6.16 (br. d, *J* = 1.9 Hz, 1 H), 4.86 (d, *J* = 2.4 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.5 (C), 150.3 (C), 140.8 (C), 132.5 (C), 131.9 (CH), 130.0 (CH), 129.5 (CH), 129.2 (CH), 128.94 (CH), 128.89 (C), 128.8 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 103.9 (C), 60.1 (CH) ppm. HRMS (ESI): *m*/*z* (%) = 408.0500/406.0507 (100.0/51.2) $[M + H]^+$; calcd. for $C_{22}H_{18}NO_2Se$: 408.0503/406.0511. The enantiomeric excess (86%) was determined by chiral HPLC (Chiralcel OD-H): hexane/*i*PrOH, 90:10, 1 mL/min, major enantiomer: t_r = 13.0 min, minor enantiomer: t_r = 23.1 min.

Typical Procedure for the Phenylsulfenyl Cyclisation of the *N*-Cbz-Protected Propargylic Amines 1: The phenylsulfenyl chloride solution was first prepared by adding sulfuryl chloride (80 μL, 1.0 mmol) to a solution of diphenyl sulfide (240.2 mg, 1.1 mmol) in 1,2-dichloroethane (3 mL) at room temperature. The solution was stirred for 5 min and the volume was diluted to 5 mL.[24] A freshly prepared 0.4 M solution of phenylsulfenyl chloride in 1,2-dichloroethane (0.375 mL, 0.15 mmol) was added to a solution of *N*-Cbz-protected propargylic amine **1** (0.10 mmol) in acetonitrile (2 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was then concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **3**.

(*S*)-4,6-Diphenyl-5-(phenylthio)-3,4-dihydro-2*H*-1,3-oxazin-2-one (3a): M.p. 158–159 °C. $[\alpha]_D^{20}$ = +328.0 (*c* = 1.00, $CHCl_3$, 87% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2 H), 7.41–7.22 (m, 13 H), 6.10 (br. s, 1 H), 4.87 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.9 (C), 150.1 (C), 140.6 (C), 133.7 (C), 131.5 (C), 130.1 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.1 (CH), 127.0 (CH), 106.8 (C), 58.8 (CH) ppm. HRMS (ESI): *m*/*z* (%) = 360.1051/361.1083 (100.0/25.3) $[M + H]^+$; calcd. for $C_{22}H_{18}NO_2S$: 360.1058/361.1092. The enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel AD-H): hexane/*i*PrOH, 90:10, 1 mL/min, major enantiomer: t_r = 12.3 min, minor enantiomer: t_r = 23.4 min.

Typical Procedure for the Phenyltellanyl Cyclisation of the *N*-Cbz-Protected Propargylic Amines 1: The phenyltelluryl bromide solution was prepared by the addition of bromine (10 μL, 0.2 mmol) to a flask containing diphenyl ditelluride (81.9 mg, 0.2 mmol) in 1,2-dichloroethane (0.4 mL) at 0 °C. The reaction mixture was stirred for 15 min at this temperature.[25] A 0.5 M solution of phenyltelluryl bromide in 1,2-dichloroethane (0.3 mL, 0.15 mmol) was added to a solution of *N*-Cbz-protected propargylic amine **1** (0.10 mmol) in acetonitrile (2 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was then concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **4**.

(*S*)-4,6-Diphenyl-5-(phenyltellanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (4a): M.p. 61–63 °C. $[\alpha]_D^{20}$ = +50.8 (*c* = 0.39, $CHCl_3$, 87% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.47 (m, 4 H), 7.43–7.39 (m, 3 H), 7.35–7.30 (m, 4 H), 7.23–7.16 (m, 4 H), 5.97 (br. d, *J* = 1.6 Hz, 1 H), 4.86 (d, *J* = 2.4 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.9 (C), 150.4 (C), 140.9 (C), 138.7 (CH), 134.4 (C), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.3 (CH), 113.0 (C), 89.1 (C), 62.5 (CH) ppm. HRMS (ESI): *m*/*z* (%): 458.0395/456.0379 (100.0/93.1) $[M + H]^+$; calcd. for $C_{22}H_{18}NO_2Te$: 458.0400/456.0382. The enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel OD-H): hexane/*i*PrOH, 90:10, 1 mL/min, major enantiomer: t_r = 13.1 min, minor enantiomer: t_r = 16.5 min.

Preparation of (*S*)-4,6-Diphenyl-5-[(*R*)-phenylsulfinyl]-3,4-dihydro-2*H*-1,3-oxazin-2-one (6a): A 30% H_2O_2 solution (10.2 μL, 0.10 mmol) was added to a solution of (*S*)-4,6-diphenyl-5-(phenylthio)-3,4-dihydro-2*H*-1,3-oxazin-2-one (**3a**; 18.0 mg, 0.05 mmol) and phenol (54 μL, 0.60 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (0.4 mL).[9a] The reaction mixture was stirred at room temperature until the disappearance of the reactant, monitored by TLC, and then the excess H_2O_2 was quenched with saturated aqueous Na_2SO_3. The phenol was neutralised with 10% aqueous NaOH. The aqueous layer was extracted with EtOAc (2× 3 mL) and the combined organic layers were dried with anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product, which was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent to afford **6a** (99% yield, 1:2.5 *dr*). Only the major diastereoisomer was characterised.

(*S*)-4,6-Diphenyl-5-[(*R*)-phenylsulfinyl]-3,4-dihydro-2*H*-1,3-oxazin-2-one (6a): M.p. 159–161 °C. $[\alpha]_D^{20}$ = +43.0 (*c* = 0.70, $CHCl_3$, 87% *ee*). ^1H NMR (300 MHz, [D_6]DMSO): δ = 8.35–8.32 (m, 2 H), 8.14 (br. d, *J* = 2.3 Hz, 1 H), 8.09–8.04 (m, 8 H), 7.92–7.77 (m, 5 H), 5.21 (br. d, *J* = 2.8 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, [D_6]-DMSO): δ = 168.4 (C), 158.9 (C), 153.8 (C), 152.5 (C), 141.9 (CH),

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141.6 (CH), 141.4 (C), 140.1 (CH), 140.0 (CH), 139.4 (CH), 139.2 (CH), 138.7 (CH), 137.3 (CH), 135.1 (CH), 130.1 (C), 63.6 (CH) ppm. HRMS (ESI): *m*/*z* (%) = 375.9906/376.9911 (100/24.4) $[M + H]^+$; calcd. for $C_{22}H_{18}NO_3S$: 376.1002/377.1036.

Computational Methods: DFT calculations were carried out by using the B3LYP[29] exchange-correlation functionals together with the standard 6-311G* basis set.[30] Optimisations were carried out by using the Berny analytical gradient optimisation method.[31] Stationary points were characterised by frequency calculations to verify that the TSs have one and only one imaginary frequency. Intrinsic reaction coordinate (IRC)[32] paths were traced to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second-order González–Schlegel integration method.[33] The solvent effects of acetonitrile were taken into account through full optimisations by using the polarisable continuum model (PCM) as developed by Tomasi and Persico[34] within the framework of self-consistent reaction field (SCRF) theory.[35] All calculations were carried out by using the Gaussian 09 suite of programs.[36]

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[26] X-ray data for compound **6a**: crystallised from ethyl acetate/*n*-hexane at 0 °C. $C_{22}H_{17}NO_3S$, M_r = 375.43, orthorhombic, space group = $P2_12_12_1$, a = 9.7840(4), b = 10.5230(4), c = 18.1390(6) Å, V = 1867.54(12) Å^3, Z = 4, $\rho_{calcd.}$ = 1.335 Mg m^{-3}, μ = 0.195 mm^{-1}, $F(000)$ = 784. A colourless crystal of 0.04 × 0.06 × 0.10 mm^3 was used; 2666 [R(int) = 0.0548] independent reflections were collected with an Enraf–Nonius CCD diffractometer by using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were re-collected at the end of the data collection to monitor crystal decay; no appreciable decay was observed. The structure was solved by direct methods and Fourier Synthesis It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97[37]). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included at calculated positions and refined riding on their respective carbon atoms. Final R(wR) values: R = 0.0520 and wR = 0.1130. CCDC-1013100 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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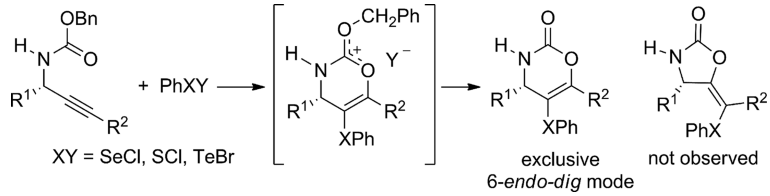

5-Chalcogenyl-1,3-oxazin-2-ones (chalcogenyl = SePh, SPh, TePh) have been synthesised in good yields and with total regioselectivity from chiral, non-racemic *N*-Cbz-protected propargylic amines through a 6-*endo-dig* cyclisation process. The experimental results have been rationalised by computational studies at the B3LYP/6-311G* level of theory.

Keywords: Cyclization / Regioselectivity / Nitrogen heterocycles / Chalcogens / Reaction mechanisms / Density functional calculations

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